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CARCINOMA OF THE JEJUNUM AND ILEUM EXCLUSIVE OF CARCINOID TUMORS

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WHEN one reviews the literature on primary carcinoma of the jejunum and ileum, one is impressed by the fact that this 20 foot (about 6 meters) segment of the intestine gives rise to less than one hundredth as many carcinomas as does the 1 foot (about 30 cm.) segment of stomach. Carcinoma of the colon and rectum is about forty times as common as carcinoma of the jejunum and ileum although the combined length of these segments of the small intestine is fully three times as great as that of the large intestine. Paradoxically, whereas it is very difficult to induce a malignant neoplasm in the stomach of animals, it may be induced readily in the small intestine of animals (29).

Because of the rarity of carcinoma of the jejunum and ileum, articles on this subject have consisted for the most part of reports of a single case or a small series of cases. Little information is available regarding criteria for the early diagnosis of this disease. In most articles on this subject, the authors have failed to separate such neoplasms as carcinoids, malignant myomas, and lymphosarcomas from ordinary carcinomas. We made a study of a relatively large series of cases of primary carcinoma of the jejunum and ileum in the hope that it would result in a more clear-cut conception of the signs, symptoms, life history, and proper treatment of this lesion.

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REVIEW OF LITERATURE

Incidence. Sorlin in 1824 wrote the first article on carcinoma of the jejunum. The first series of malignant lesions of the small intestine was reported in 1876 by Leichtenstern. They formed 0.095 per cent of the malignant lesions of the entire gastrointestinal tract. Maydl reported 0.029 per cent for this ratio, while Nothnagel found 0.051 per cent. Brill reported 2.3 per cent of intestinal malignancies were in the small intestine and Hinz agreed with Ewing in reporting 3.08 per cent. Rankin and Mayo in 1930 reported 0.62 per cent of gastrointestinal malignancies were in the small intestine. Raiford in 1932 reported 4.9 per cent for this ratio, while Forgue and Chauvin in 1915 found 6 per cent. Christofferson and Jacobs in 1939 found 1.6 per cent in the same comparison.

After careful review of the literature more than 500 cases of adenocarcinoma of the jejunum and ileum were found.

Age and sex incidence. Duncan's case of carcinoma of the ileum in which the patient was

a child, aged 3½ years, is the youngest in the literature. Soper in 1909 stated that the average age for this lesion was 46.5 years with a 2:1 sex ratio of male to female. Mayo in 1940, quoted 52.6 years as the average age, the males being involved two and a half times as often as the females.

Signs and symptoms. In 1903 Nothnagel observed that the symptoms of this disease are similar to those seen in patients with lesions of the proximal portion of the colon. He stated that when these tumors are palpable, they are the most movable of all intestinal carcinomas. Shallow and his associates in 1945 stated that 75 per cent of these lesions are palpable. Lahey in 1915 wrote that vomiting depends on the extent of obstruction. Johnson in 1921 summarized the symptoms and signs of tumor of the small intestine and gave a more definite picture of this condition than had previously been presented in the literature.

In 1930 Rankin and Mayo found that the average duration of symptoms was about 14 to 15 months and that the signs and symptoms are directly related to chronic intermittent intestinal obstruction. They emphasized the importance of roentgenologic examination and anemia, as Bargen and Balfour had previously done. They described the abdominal mass as "slipping away from the fingers." Constipation and loss of weight were frequent. Mayo stated in 1940 that 30.8 per cent of jejunal malignant lesions and 20 per cent of ileac malignant lesions were diagnosed as such preoperatively.

In 1931 Harris and Rosenblum reported a jejunal lesion with localized referred back pain, a point which had not previously been mentioned. Horsley (23) and Rivers and Roodenburg explained the mechanism of this pain.

Roentgenographic findings. Soper in 1909 first emphasized the importance of roentgenographic examination while Portis and Portis in 1923 and Clark in 1927, employing their methods, made early diagnoses of this lesion. Henceforward most authors mentioned the value of roentgenographic examinations. Golden, using roentgenographic technique, differentiated between malignant and inflammatory lesions.

Carter and Deacon found the results of 82.6 per cent and 25 per cent respectively of their examinations of the small bowel, to be positive; Weber and Kirklin found that 85 per cent of jejunal lesions and 67 per cent of ileac lesions were diagnosed roentgenologically. The latter authors emphasized that the roentgenographic examination was the cardinal maneuver whether the contrast medium had been administered orally or rectally. In a recent comment, Weber stated that 90 per cent of lesions of the small bowel should at least be suspected on the basis of an adequate roentgenologic examination of the intestine.

Pathology. Nothnagel in 1903 suggested that these lesions be classified into 4 categories: (1) carcinoma adenomatosum simplex, (2) carcinoma adenomatosum medullare, (3) scirrhous carcinoma adenomatosum, (4) colloid carcinoma adenomatosum. Judd in 1919 considered these lesions to be annular lesions or malignant degenerated polyps, while Johnson in 1921 described 4 gross types; namely, (1) the ring form, (2) the polypoid type, (3) the ulcerating types, and (4) the colloid types. Ewing's frequently quoted classification was (1) a lesion originating in local or general polyposis, (2) a localized adenocarcinoma with carcinomatous variation in structure, and (3) carcinoid tumor. Bell wrote that there were two distinct types: carcinoma and an argentaffin tumor.

Treatment and prognosis. Keyser in 1908 recommended wide resection of the lesion, while Lahey and Judd additionally advised enteroenterostomy for inoperable lesions. Ochsner and Horsley refined the surgical techniques. Wangensteen stated that he was increasing his indications for primary resection, but he warned that the distention of the intestine must be controlled. Carter; Mayo in 1940; Ochsner and Mahorner; Shallow, Eger and Carty; Wangensteen and others emphasized the importance of preoperative and postoperative care.

The operative mortality rate as quoted by Venot and Parcelier, Hellstrom, Carter, and Mayo and Nettrour varied from 43.4 per cent to 30 per cent, while the average postoperative length of life varied from 11 months to 17.3 months.

PRESENT SERIES

Material and methods. The files of surgical pathology of the Mayo Clinic were studied for cases in which the diagnosis of carcinoma of the small intestine had been made. Several hundred cases were so listed from January, 1907, through June, 1947. Carcinomas of the duodenum were first excluded from the study inasmuch as these had been previously reported as a group by Lichtman (11) and his associates. Deleted next were carcinoids, which had been reported in 1943 by Dockerty and Ashburn and resurveyed in 1948 by Ashburn. From the clinical history and the surgical and necropsy protocols it became possible to exclude metastatic lesions. Leiomyosarcomas (40) and lymphosarcomas (17) were ruled out by collaboration with several fellows of the Mayo Foundation who were currently working on these topics.

The residual group comprised 63 cases in which the lesion was considered by the pathologist to be primary adenocarcinoma of the jejunum or of the ileum. Fifty-two of these cases had been reported by Mayo in 1940. All specimens had been preserved in 10 per cent solution of formalin.

The gross specimens were secured and studied in detail with reference to the site, size, and mesenteric relations of the growths. Evidences of perforation, inflammation and cystic degeneration were carefully sought out. Special attention was directed to the presence or absence of peritoneal, mesenteric, and lymph nodal involvement by the carcinoma. The gross types of the lesions were charted as ulcerated, polypoid and "napkin ring." Observations were made on the cases in which obstruction occurred as to the cause of the obstruction, whether it was due to obliteration, intussusception or simple fibrosis as seen in scirrhous growths.

After as careful a gross inspection as possible had been made and the findings had been tabulated, the specimens were sectioned at various levels and an additional endeavor was made to assay the degree and character of any malignant infiltration beyond the confines of the bowel, it being considered possible that some modification of Dukes's classification of carcinoma could be applied.

TABLE I.—PRIMARY ADENOCARCINOMA OF THE JEJUNUM AND OF THE ILEUM: AGE AND SEX DISTRIBUTION OF PATIENTS

Age, years	Total cases	Jejunum			Ileum		
		Total	Male	Female	Total	Male	Female
20–29	4	3	3	0	1	0	1
30–39	7	5	3	2	2	2	0
40–49	19	13	7	6	6	3	3
50–59	19	14	9	5	5	2	3
60–69	12	9	6	3	3	1	2
70–79	2	0	0	0	2	1	1
Total	63	44	28	16	19	9	10
Mean age, years	49.2	47.8	45	52.4	52	50.4	53.4

Selected blocks of tissue were then removed from the growths, the overlying portion of the peritoneum, the mesentery and any available lymph nodes. These blocks, averaging four or five per case, were placed in fresh 10 per cent solution of formalin, sectioned by the freezing method and stained routinely with hematoxylin and eosin. Some 300 slides thus became available for microscopic study.

Forty-four tumors were of jejunal and 19 were of ileac derivation.

Age and sex incidence. The youngest patient in the series was 24 years of age; the oldest patient was 75 years. The average age for the patients with jejunal lesions was 47.8 years, while the average age for the patients with the ileac lesions was 52 years. The average age for the combined groups was 49.2 years. A larger number of patients were in the fifth and sixth decades in both jejunal and ileac series than in any other ten year period. This is shown in Table I in relation to the sex incidence.

The male to female sex ratio approached a 2:1 figure in cases of carcinoma of the jejunum, while the number of patients of each sex with carcinoma of the ileum was almost equal. The history of pre-existing conditions such as typhoid fever, tuberculosis, chronic ulcerative colitis, and adhesions was tabulated, but the relationship to the development of adenocarcinoma was not considered significant. Two of the patients who had jejunal carcinoma were brothers having 6 years' difference in their ages, who underwent operation within a

TABLE II.—CLINICAL SYNDROMES

Site	Total	Anemic syndrome			Obstructive syndrome			Perforative syndrome		
		Cases		Duration, months	Cases		Duration, months	Cases		Duration, months
		No.	Per cent		No.	Per cent		No.	Per cent	
Jejunum	44	29	66	11	31	70	9	6	14	5
Ileum	19	14	74	6.4	15	79	6.3	4	21	3.5
Total	63	43	68	10	46	73	8	10	16	4.5

year of each other at the Mayo Clinic. One of the brothers had an adenocarcinoma of the jejunum, grade 3 (Broders' method), while the other had a lesion of grade 4. This was the only instance of a familial tendency in this series.

Clinical signs and symptoms. In reviewing the records of the 63 patients who had primary adenocarcinoma of the jejunum and ileum, the symptoms seemed best divided into three complexes, namely: the anemic syndrome, the obstructive syndrome, and the perforative syndrome.

In the anemic group fatigability, weakness, continued tiredness, shortness of breath on exertion, and other symptoms related to anemia were some of the patients' presenting symptoms. Sixty-six per cent of the patients with jejunal lesions gave one or more of these symptoms related to anemia with an average duration of 11 months at the time they were seen at the clinic. Seventy-four per cent of the 19 patients with ileac lesions gave one or more of these symptoms related to anemia, with an average duration of 6.4 months at the time they were seen at the clinic.

Features suggesting obstruction of the small bowel, partial or complete, composed the most common picture seen, and this was responsible for more clinically suspected diagnoses than any other syndrome. Among the patients with jejunal lesions, 70 per cent demonstrated some degree of partial or complete obstruction of the small bowel. The duration of these symptoms varied from 1 month to 4 years with an average duration of symptoms of 9 months. In the series of ileac cases 79 per cent of the patients showed either partial or complete obstruction with an average duration of symptoms of 6.3 months. Intermittent cramping abdominal pain relieved by vomiting was the most common symptom in patients with intestinal obstruction. The abdominal pain varied in location, severity, and character. It was described variously as "cramplike," "cutting," "shooting," "piercing," "tearing" and "generalized soreness." The vomiting varied from the immediate regurgitation of everything ingested, as seen in complete intestinal obstruction, to occasional vomiting 12 to 18 hours after the eating of large meals. Some of the early signs of incomplete obstruction of the small bowel such as recurrent waves of nausea without vomiting, a feeling of weakness, an unnatural feeling of awareness that all was not well, and other indefinite symptoms were occasionally elicited. As the disease progressed from these early symptoms, the attacks of vomiting after eating became more severe and lasted longer until obstruction occurred and neither food nor fluid could be retained. The abdominal pain likewise usually became more severe and sharper as the disease progressed. As vomiting became worse the patient became afraid to eat and a vicious cycle was established which increased anemia, dehydration and electrolytic unbalance. The patient sometimes resorted to sticking a finger down his throat to obtain a sense of relief after meals.

A palpable mass was present in the jejunum in 41 per cent of the cases and in the ileum in 48 per cent of the cases. The location of the mass in the jejunum was predominantly in the left lower abdominal quadrant, whereas in the ileum only very few were in the left lower quadrant, more than two thirds of the masses being located in the right lower quadrant. Visible peristalsis was noted by the physician in 33 per cent of the ileac series and in 26 per cent of the jejunal series. Borborygmus was present in 50 per cent of cases of entire series.

TABLE III.—CLINICAL SIGNS

Site	Total cases	Cases with mass	Cases with visible peristalsis	Average loss of weight; average duration	Cases with constipation; average duration
Jejunum	44	41 per cent	26 per cent	26 pounds 11 months	55 per cent 5.7 months
Ileum	19	48 per cent	33 per cent	25 pounds 8 months	42 per cent 7.2 months

In these cases included in the perforative syndrome group the patients had definitely localized referred pain. The lesion had perforated the bowel wall and involved the parietal nerves; that is, the spinal somatic nerves were utilized in addition to the usual pathway of the sensory fibers in the splanchnic branches of the sympathetic nerves. In these cases the symptoms caused by involvement of the parietal nerves completely masked the mild vague symptoms more commonly produced in the usual cases. Six patients (14 per cent) with carcinoma of the jejunum had symptoms of referred pain for an average duration of 5 months. Four of these had pain referred to the shoulders, while 1 had a well localized pain referred to his back, and another had a localized pain in the upper right abdominal quadrant in addition to poorly localized paraumbilical pain. Three patients in this group stated that they experienced relief from lying on their right sides. Some obtained relief by passing flatus or having a bowel movement and most noted temporary relief after vomiting. On the other hand, 4 (21 per cent) of the patients with carcinoma of the ileum had symptoms of the perforative syndrome with an average duration of 3.5 months. One patient had a constant pain in the left lower quadrant of the abdomen which extended to the testicles. Another patient had a localized back pain, and the third patient had a well localized continuous pain in the left lower quadrant of the abdomen in addition to the poorly localized paraumbilical pain. The last patient had a pain which extended from the right lower quadrant of the abdomen to the left groin and which was made worse by lying on the right side. Table II compares the 3 clinical syndromes of carcinoma of the jejunum to those of carcinoma of the ileum.

Thirty-three per cent of the patients with jejunal lesions complained of passing excessive flatus or belching gas, while only 16.6 per cent in the ileac group complained of these symptoms. In 55 per cent of the jejunal cases constipation had been present for an average duration of 5.7 months; in 42 per cent of the ileac cases constipation had been present for an average duration of 7.2 months. The incidence of melena was recorded, but it was not considered an accurate index to bleeding from the small bowel because extraneous causes for bleeding could not be adequately eliminated; therefore, the findings on melena were omitted.

As regards the physical examination the presence of a palpable mass, anemia and visible peristalsis have been mentioned previously. Visible peristalsis was almost pathognomonic of obstruction of the small bowel; however, it was usually necessary to see the patient several times before this was observed. Distention of the abdomen was infrequently recorded. The loss of weight up to the time of diagnosis was about the same for the jejunal cases as for those with neoplasm in the ileum, averaging about 25 pounds (about 11 kgm.). The average period over which the patient lost weight was a little longer in the jejunal cases (11 months) than in the ileac cases.

Table III includes data on the signs in jejunal and ileac carcinomas.

In 3 cases a nodular mass was felt on rectal examination in the jejunal series, while 2 such masses were noted in the ileac group in addition to 2 cases with palpable supraclavicular nodes. Biopsy was not performed on any of these nodes.

Roentgenologic and laboratory findings. An attempt was made to evaluate the efficacy of roentgenologic examination. No roentgenologic studies of the small bowel were made in these cases before 1927. Since 1927 examinations of the small bowel have been done in 19 cases. In 1 case the diagnosis was missed; in 18 cases the diagnosis of "carcinoma," "tumor" or "lesions" in the appropriate part of the small intestine was correctly made. Figure

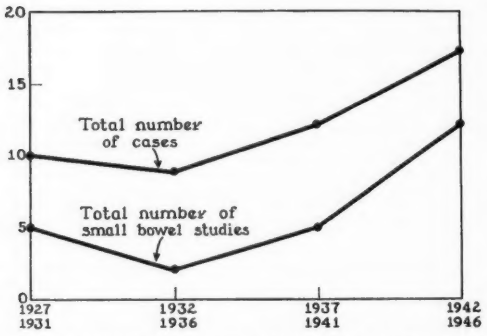

Fig. 1. Number of roentgenologic studies of the small bowel related to the total number of cases from 1927 through 1946.

1 demonstrates the number of roentgenologic studies of the small bowel done in relation to the total number of cases from 1927 through 1946. In the last 5 years which this paper includes (1942 through 1946), roentgenologic studies of the small bowel were made in 76.5 per cent of the cases and 92.3 per cent of these studies were diagnostic. In 13 additional cases not included in Figure 1, roentgenologic studies of the colon or stomach were helpful in directing attention to the small intestine.

It is interesting that 3 patients in the jejunal series and 2 patients in the ileac series had been treated for anemia alone for several months before coming to the clinic. The average concentration of hemoglobin was 70 per cent of normal in the jejunal group and 67 per cent in the ileac group. The average erythrocyte count per cubic centimeter was 4,000,000 in the jejunal group and 4,500,000 in the ileac series. Therefore, there was hypochromic anemia in both series.

The examination of the gastric contents revealed a variation in free hydrochloric acid from zero units to 60 units, with an average of 22 units in the jejunal series. The patients with ileac neoplasm showed the variation from zero units to 76 units of free hydrochloric acid with an average of 26 units.

The blood urea and carbon dioxide combining power of the blood were determined in only a few cases, so that the figures would not be significant.

Pathologic findings. Table IV shows the location of the lesions. In the jejunal group 31 lesions were in the upper third; 5 lesions were in the middle third; 3 lesions were in the lower third; in 5 cases the exact location was not ascertained. In the ileac series 13 of the lesions were in the lower third of the ileum and in 6 cases the exact location was not definitely ascertainable from operative notes.

The lesions were divided grossly into three types, namely: the annular constricting type, the irregular ulcerative type and the polypoid type. In the jejunal group there were 30 of the first type, 8 of the second type, and 3 of the third type, 3 patients having an undetermined gross type. The ileac lesions showed 6 annular constricting lesions, 3 irregular lesions and 3 polypoid lesions, while in 7 cases the gross type was undetermined owing to mutilation of the specimens from previous studies. The average size for the annular constricting lesions was 4 by 4 by 3 centimeters, the irregular ulcerative lesions averaged 9 by 6 by 6 centimeters and the polypoid lesions averaged 6 by 5 by 5 centimeters.

There was obstruction of varying degree with dilatation and hypertrophy of the bowel wall above the lesion and relative constriction below it in all specimens. Two lesions seemed to occur in a diverticulum in the jejunum. Stercoral ulcers were not observed in any cases. Perforation of the bowel wall occurred 6 times in the ileac cases and 15 times in the jejunal series or in a third of the combined series.

Intussusception occurred in 3 cases in the jejunal series and in 2 cases in the ileac group.

TABLE IV.—LOCATION OF LESIONS IN JEJUNUM AND ILEUM

Site	Total	Upper third		Middle third		Lower third		Unknown	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Jejunum	44	31	71	5	11	3	7	5	11
Ileum	19	0	0	0	0	13	68	6	32

In 4 of these cases the lesion was of the polypoid type; in the other instance the gross type was undetermined.

In the surgical notes the liver was stated to be involved in 6 cases, in 4 of which ascites was present. Supraclavicular nodes were reported as being palpable in 2 cases and in 1 of these cases a rectal shelf was felt. A Krukenberg-like tumor of the ovary was found in 3 instances. Tissue was not available from all of these areas.

Tissue was available in adequate amounts for microscopic study in all cases. Hepatic tissue for biopsy was the only specimen in 2 cases. Sections were made from all available nodes and studied microscopically. The lesions were graded according to Broders' method and Dukes's classification was also applied. In the ileac group nodes suspected of showing metastatic carcinoma were found in 15 cases and in 12 of these cases the tissue proved microscopically to be positive. In the jejunal group 32 cases were suspected of showing metastatic nodes and in only 21 cases were the nodes proved to be positive on microscopic examination, 11 patients having inflammatory nodes only.

In all 34 cases of lesions of grades 3 and 4 the serosa of the bowel was involved microscopically and only 3 cases in the ileac series, grades 1 and 2, were type A lesions. Sixteen of the low grade lesions were type B, while 12 of the high grade lesions were type B, according to Dukes's classification. It is obvious that the lymph nodal involvement is related to the grade of malignancy, varying from 20 per cent nodal involvement in grade 1 lesions to 81.0 per cent nodal involvement in the grade 4 lesions. Thirty-five per cent of the nodes suspected of malignancy grossly were found to be inflammatory in the jejunal series, while 20 per cent of such nodes were inflammatory in the ileac series.

In the jejunal series there were 2 grade 1 lesions, while in the ileac group there were 3 such lesions. The grade 1 lesions in an adenoma which showed no infiltration of the submucosa were omitted. One of the grade 1 lesions showed especially well the microscopic infiltration of the carcinomatous cells into the muscular coat of the bowel. In the typical

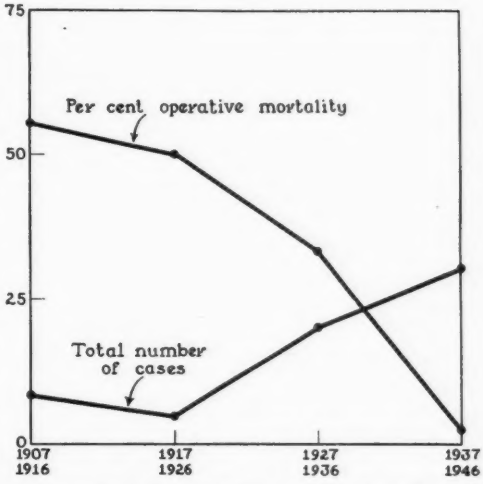

Fig. 2. Operative mortality rate related to the total number of cases from 1907 through 1946.

grade 1 lesions the glandlike formation contained well differentiated cells with the nuclei at the basement membrane. One lesion in the ileum was a scirrhous adenocarcinoma. There was an unusually large amount of dense fibrous tissue between the acini, and the cells were in strands which recalled the microscopic picture of scirrhous adenocarcinoma of the stomach.

There were 24 grade 2 lesions, 20 being in the jejunum and 4 being in the ileum. The glandular formation was similar to that seen in the grade 1 lesions, but there was less differentiation in the individual cells and the glandlike formation was not so perfect as in the grade 1 lesions. One case well demonstrated invasion of a vein by carcinomatous cells (Fig. 3). Involvement of vessels and nerves was looked for on each of the slides, but several slides were made in each case and this precludes an accurate statistical report of these findings. Selective involvement of the myenteric plexus was seen in several cases (Fig. 4). One lesion was a scirrhous adenocarcinoma similar to the one described previously and 1 was a typical mucous adenocarcinoma.

Thirteen of the lesions were grade 3, 9 being in the jejunum and 4 being in the ileum. The pattern varied from one in which there was an

TABLE V.—OPERATIVE PROCEDURES IN JEJUNUM AND ILEUM

Site	Total cases	Resection		Palliative		Exploration		Operative mortality rate, per cent
		No.	Per cent	No.	Per cent	No.	Per cent	
Jejunum	44	32	73	9	20	3	7	16.0
Ileum	19	13	68	3	16	3	16	36.8
Total	63	45	71	12	19	6	10	22.0

TABLE VI.—ADENOCARCINOMA OF THE JEJUNUM AND ILEUM: SURVIVAL RATES ACCORDING TO SITE*

Site	Patients		Lived 3 or more years after operation		Patients		Lived 5 or more years after operation		Patients		Lived 10 or more years after operation	
	Total	Traced	No.	Per cent of traced patients	Total	Traced	No.	Per cent of traced patients	Total	Traced	No.	Per cent of traced patients
Jejunum	36	32	12	37.5	32	29	8	27.6	22	21	3	14.3
Ileum	19	18	5	27.8	17	17	3	17.6	11	11	1	9.1
Total	55	50	17	34.0	49	46	11	23.9	33	32	4	12.5

*Inquiry as of January 1, 1948. The 3 year group includes only those patients operated on 3 or more years prior to the time of inquiry, that is, 1944 or earlier; the 5 year group includes only those patients operated on in 1942 or earlier; the 10 year group includes only those patients operated on in 1937 or earlier.

attempt at glandular formation to a picture in which there was no attempt at glandular formation. Figure 5 demonstrates the latter type. The cells are grouped in irregular islands with small amounts of connective tissue between them, and the individual cells show a loss of polarity. Two mucous adenocarcinomas were found in this group. The so called bird's eye cells are easily identified, as are the large globular cells in which the mucus has compressed the nuclei to signet ring shape. Around the masses of neoplastic cells either small or large spaces are often formed containing mucus which has the appearance of colloid after the tissue has been stained.

There were 21 grade 4 lesions, 13 being in the jejunum and 8 being in the ileum. The cells were highly undifferentiated and showed poor polarization and varying staining characteristics with a similar variation in the size and shape of the nucleus. Mitotic figures were frequent. Four mucous adenocarcinomas were found in this group. Figure 6 shows typical signet ring cells so characteristic of this type of growth. The gross picture of this lesion is shown in Figure 7.

In general, it may be said that the larger the lesion, the greater the incidence of nodal involvement and the higher the grade of the lesion. However, this was not always true.

Treatment and prognosis. Wide resection of the lesion and regional nodes was performed in 73 per cent of the jejunal and 68 per cent of the ileac cases. Palliative procedures were performed in 20 per cent and 16 per cent of the jejunal and ileac cases respectively. Exploratory operation alone was performed in 7 per cent of the jejunal and in 16 per cent of the ileac group. The operative mortality rate of all surgical procedures was 16.0 per cent in the jejunal group and 36.8 per cent in the ileac group (Table V). However, the over-all operative mortality rate varied from 55.5 per cent in the first decade covered by this paper to 3.2 per cent in the last decade (Fig. 2).

There were 45 lesions resected with hope of cure and 36 patients in this group survived the procedure. Forty-nine patients were operated on prior to 1943; 3 of these patients could not be traced. Of the 46 patients who underwent resection prior to 1943 and who were traced, 11 (23.9 per cent) survived 5 or more years.

The 3, 5 and 10 year survival rates may be compared in Table VI. Three patients who had adenocarcinoma of the jejunum lived for 10 years postoperatively; 1 lesion was grade 4,

Fig. 3. Grade 2 adenocarcinoma of the jejunum. Note the invasion of the vein by the carcinomatous cells (hematoxylin and eosin, ×37).

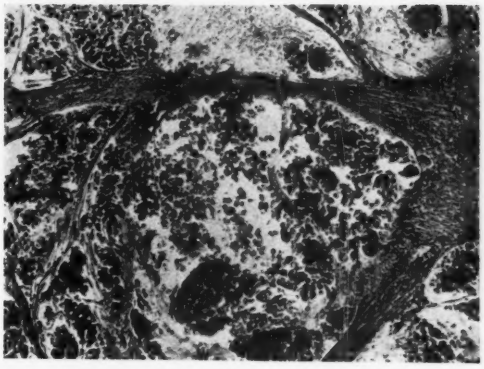

Fig. 5. Grade 3 adenocarcinoma of the jejunum showing a highly malignant tumor with no pattern of arrangement for the cells (hematoxylin and eosin, ×75).

while 2 were grade 2. In the ileac series only 1 patient lived 10 years or more after operation; the lesion was grade 1. Eight of the jejunal patients lived 5 or more years. Seven lesions were grade 2 and 1 was grade 4. In the ileac group 3 patients lived 5 or more years; 1 case was grade 2 and 2 cases were grade 1. Twelve jejunal patients lived 3 years or more; 8 lesions were grade 2, 2 were grade 3, and 2 were grade 4. Five ileac patients lived 3 years or more; 2 lesions were grade 1, 2 grade 2 and 1 grade 4. In the jejunal series there have been 25 cases since 1935 with no hospital deaths and 6 such cases since 1939 in ileac series.

Fig. 4. Grade 2 adenocarcinoma of the jejunum showing selective involvement of the myenteric plexus (hematoxylin and eosin, ×90).

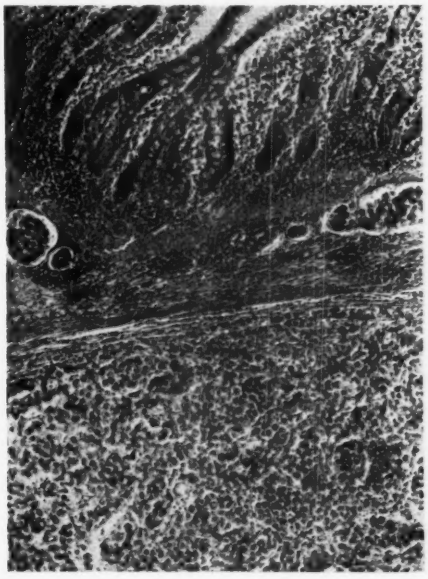

Fig. 6. Grade 4 mucous adenocarcinoma of the ileum. Note the typical signet ring cells so characteristic of this type of growth (hematoxylin and eosin, ×90).

Fig. 7. Grade 4 mucous adenocarcinoma of the ileum. Note the dilatation above the lesion and the normal width of the bowel below the lesion. The microscopic picture of this lesion is shown in Figure 6.

The average postoperative duration was 30.8 months in the jejunal and 34.8 months in the ileac series. The postoperative duration was compared to the grade of the lesion and nodal involvement, as seen in Table VII.

TABLE VII.—CORRELATION OF THE POSTOPERATIVE DURATION OF LIFE WITH THE GRADE OF THE LESION AND THE NODAL INVOLVEMENT

Grade	Cases	Lymph nodal involvement		Average postoperative duration of life, years*	Operations
		No.	Per cent		
1	5	1	20.0	5.33	4 resections 1 palliative
2	24	9	37.5	3.13	20 resections 2 palliative 2 exploratory
3	13	6	46.2	1.65	6 resections 3 palliative 4 exploratory
4	21	17	81.0	1.24	15 resections 6 palliative

*Eleven patients in this series were still living at the time of this report; these figures therefore represent minimal duration of life.

SUMMARY AND CONCLUSIONS

Adenocarcinomas of the small intestine at the Mayo Clinic (4) in recent years form about 1 per cent of the carcinomas of the gastrointestinal tract including the stomach and rectum. In the literature this incidence was found to be uniformly low, but also was found to vary a relatively large amount. This was due chiefly to lack of definition of terms and lack of pathologic verification of lesions. Only about six articles and no large series of cases have been reported in which carcinoid tumors were separated from adenocarcinoma of the jejunum and ileum. This report is made to segregate definitely these two types of lesions and to show the clinical, pathologic, and surgical results of adenocarcinoma. There were 63 microscopically proved adenocarcinomas of the jejunum and ileum from 1907 through 1947, at the Mayo Clinic. Forty-four lesions were in the jejunum and 19 were in the ileum. The average age for entire group was 49.2 years. The two sexes were affected equally in the ileac series, while men were affected about twice as often as women in the jejunal group.

The symptoms of these patients are best divided into three symptom complexes as follows: the anemic syndrome found in 68 per cent of cases, the obstructive syndrome found in 73 per cent of cases, and the perforative syndrome found in 16 per cent of cases. The occurrence of constipation, loss of weight, and belching or the passing of flatus is mentioned because of its frequency. Visible peristalsis and the palpation of an abdominal mass are the two most important signs on physical examination.

Anemia, which appeared to be chiefly due to bleeding from the intestinal tract, was usually present.

The advance of roentgenology in studying the small intestine has been dramatic in the last 20 years. In the last 5 years which this paper includes, roentgenologic studies of the small bowel were made in 76.5 per cent of the cases and 92.3 per cent of these studies were diagnostic.

In general, the size of the tumor was proportional to the grade of the lesion. Generally the nodal involvement was directly related to the grade of the lesion. There were more high grade lesions than low grade lesions. There were also several large high grade lesions with no nodal involvement, which lends support to the idea that tumors may be fundamentally of two types regardless of grade; usually, those which spread by extension and those which spread by vascular routes. The number or size

of nodes present at operation is not a reliable index to microscopic nodal involvement. Intussusception occurred 5 times and is usually found in the presence of a polypoid type of lesion. Perforation of the bowel wall was found in a third of the cases. Neoplastic involvement of the liver occurred 6 times and distal metastasis was also rare in this series of cases.

Wide resection of the lesion with removal of regional lymph nodes is the treatment of choice. A palliative short circuiting operation to divert the fecal stream around the growth is of value, if resection is impossible. The operative mortality rate for the entire series from 1907 through June, 1947, was 22.0 per cent. The absence of any postoperative deaths in the 25 jejunal cases since 1935 and in the 6 ileac cases since 1939 demonstrates chiefly how the improvement in preoperative and postoperative care and the advent of chemotherapy have played their role in the treatment.

In general, the higher the grade of the lesion and the greater the percentage of nodal involvement, the worse is the prognosis of the patient. The average duration of life of the patients for the entire series was 32.2 months. The prognosis in the case of the ileac lesions was slightly better than that in the case of the jejunal lesions.

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AN APPRAISAL OF THE OPERATION OF ANTERIOR RESECTION FOR CARCINOMA OF RECTUM AND RECTOSIGMOID

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SOME years ago, there occurred in this country a revival of old operative procedures designed to preserve normal sphincteric action in the treatment of cancer of the rectum and rectosigmoid. Prior to that time the important contribution of Miles, with respect to the three zones of spread from the original tumor site, was a major factor in the almost universal adoption of the operation of abdominoperineal resection. However, when Westhues, in 1934, using the more efficient Spalteholz clearing method, reported only 1 instance in 74 cases of spread to lymph nodes *distal* to the tumor site and when this work was confirmed by Klein working in our laboratories at Mt. Sinai Hospital, Coller and his associates, and David and Gilchrist and others, there developed in some clinics considerable doubt as to the necessity for carrying out as radical an operation as abdominoperineal resection in *every* instance of cancer of the rectum and rectosigmoid. Consequently, old operations were revived, modified, and improved with the purpose of carrying out a good operation for cancer and at the same time preserving the sphincter muscles. It is probable that the advent of the antibiotics at about this period was an added incentive to the development of the sphincter-saving operations. Evidence was accumulating to substantiate the view that operative mortality rates were dropping in the surgery of colonic cancers with the more extended use of sulfonamides and the newly discovered penicillin. The operation of anterior resection was perfected mainly by Dixon and Wangensteen. The chief proponents of the posterior resection operation have been Babcock and Bacon.

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Although we have been strong proponents of the operation of abdominoperineal resection for many years and have frequently stated that sentimental considerations for the anal sphincters should never deter the surgeon from carrying out as radical an operation for cancer as he could perform to offer each patient every possibility of a cure, we decided in 1943 to employ the operation of anterior resection in a series of patients in order to appraise the efficacy of the procedure as a radical operation. It must be admitted that we were hesitant to initiate this experiment because it meant the temporary abandonment of a time-honored, thoroughly efficient operative procedure and the possibility of withholding from some patients, at least, the sole chance of cure. Surgical progress would indeed cease if the philosophy of trial, error, and change were altogether abandoned. This paper, therefore, presents our experience with 163 patients who were treated for cancer of the rectum and rectosigmoid by utilizing the operation of anterior resection. We believe that the results reported herewith clearly indicate the place that this operation should occupy in our therapy of this disease and definitely establish the limitations of the procedure.

Judging from the diversified descriptions in the literature, there seems to be no unanimity of opinion as to the exact location of the rectosigmoid. It is to be observed that the loose use of the phrase "peritoneal reflection" is probably responsible for this diversity of opinion. Some authors state that the site of reflection of the anterior rectal peritoneum to the bladder in the male and the vagina in the female marks the position of the rectosigmoid. Others, more accurately, place the site of "peritoneal reflection" laterally to the pelvic wall at the point where the mesosigmoid

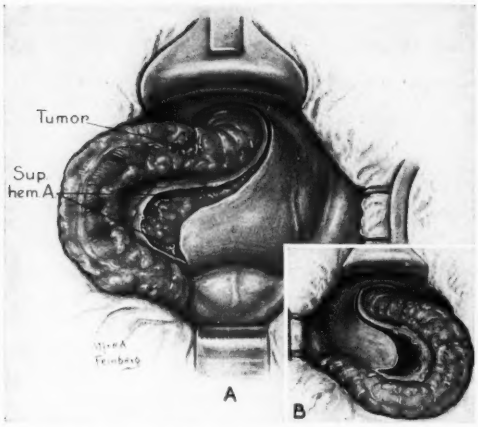

Fig. 1. Tumor of rectosigmoid. Incision of lateral and anterior peritoneum and ligation of superior hemorrhoidal vessels.

ceases to exist. There is also considerable variation in the literature as to the distance between the anus and the rectosigmoid as measured by sigmoidoscopic examination. This varies between 9 and 15 centimeters. It must be apparent that it is of considerable importance that this feature of the whole problem be clarified because the utilization of the operation of anterior resection is in large part connected with the anatomical location of the rectosigmoid. We emphasize this point because it has loomed large in the conclusions we have reached in this study. On the basis of a large operative experience and many hundreds of sigmoidoscopic observations, we believe that the surgical rectosigmoid is located at that area of the bowel where the mesosigmoid ceases to exist as such, where the peritoneum, instead of encircling the bowel, leaves the posterior and lateral aspects and merges with the pelvic peritoneum, and where the inferior mesenteric vessels, now the superior hemorrhoidals, leave the mesentery of the sigmoid colon and lie behind the bowel. In most individuals this point of convergence lies opposite the second or third sacral segment. In the person of average height and average-shaped pelvis, the rectosigmoid, in our experience, is located between 6 and 8 inches from the anal margin. In squat individuals, the pelvis is more shallow and the distance, consequently, shorter. Tall lanky persons may present a deep pelvis with a greater measurable distance from anus to rectosigmoid. Recently we have measured the exact location of the rectosigmoid at the operating table. A calibrated rectal bougie is inserted into the rectum and after the abdomen is opened, its tip is projected to the exact location of the rectosigmoid. The site of emergence at the anal margin is marked and measured after the bougie is withdrawn. We are emphasizing this feature in the anatomy of the region because of its importance to the problem under discussion.

This study has shown that, other than the location of the carcinoma in the rectum with respect to distance from the anal margin and

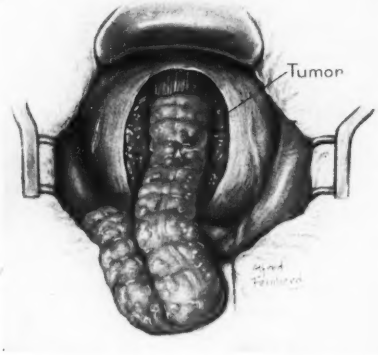

Fig. 2. Preparation of peritoneal flaps. Rectum has been mobilized from pelvic attachments.

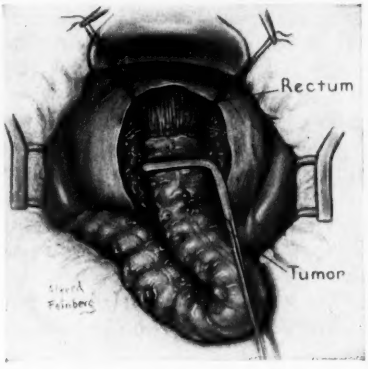

Fig. 3. Guy sutures placed on each side of rectum below point of transection.

the results of follow-up studies, there are no preoperative or operative criteria which can guide the surgeon in choosing between anterior resection and the abdominoperineal operation. The classification of Dukes has not been too helpful to the surgeon at the operating table. It is, however, of unquestionable value to the pathologist and has its largest field of applicability in appraising long term results of surgical therapy. By the same token, it has been difficult, in the experience of many observers, to correlate the Broders histological classification with the selection of the operative procedure in each instance. There seems to be almost universal agreement that the surgical procedure should not be based entirely on the histological grading of the biopsy specimen.

The size and gross type of a rectal cancer cannot be used as an indication of spread to regional lymph nodes or criterion for selection of a particular operative procedure. Our experience confirms the findings of other observers that the large polypoid tumors projecting toward the lumen are less malignant than the infiltrating variety. A small sessile tumor certainly presents a more hopeful picture in the gross and may tempt the surgeon to choose an operative procedure to preserve the sphincter muscles solely because of the flatness and small size of the growth. Experience, however, has shown that this variety of carcinoma of the rectum has the highest incidence of regional lymph node spread and probably the greatest percentage of local recurrence. The large size of a lesion should not deter the surgeon from exploring to determine operability. Many more will be found resectable than otherwise.

The finding at operation of penetration of the lesion to the serosa with local peritoneal

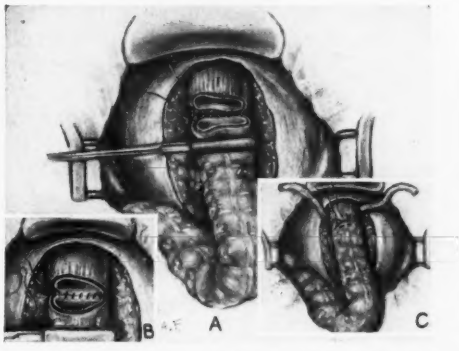

Fig. 5. Details of anastomosis. Fine chromic catgut for mucosa and interrupted fine silk for outer layer. One cigarette drain placed to bottom of pelvis on each side of rectum.

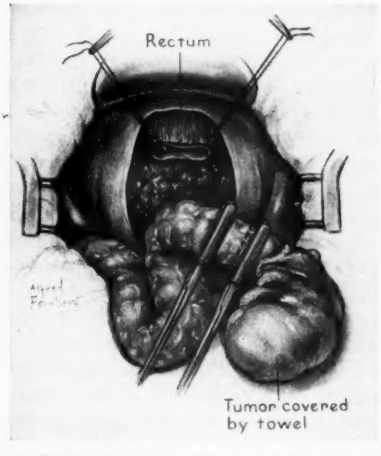

Fig. 4. Point of section at least 2 inches below tumor and well proximal to it thus insuring removal of lower mesosigmoid as well.

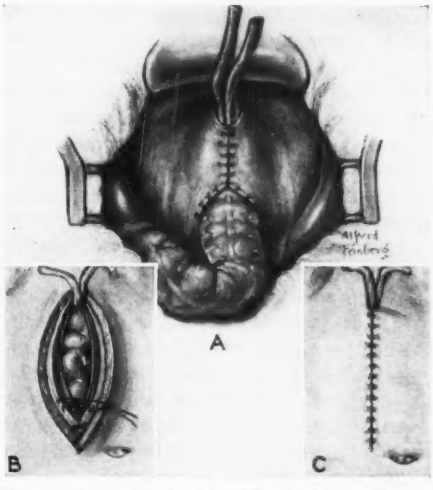

Fig. 6. Reconstruction of pelvic diaphragm above the anastomosis. Emergence of drains at lower angle of wound which is closed with buried figure of 8 stainless steel wire sutures and clips.

implants or gross involvement of the rectal fat calls for an operation of the most radical variety. There can be no compromising in a situation of this sort. However, it must be admitted that the incidence of recurrence under such circumstances is probably just as great with the abdominoperineal operation as with anterior resection.

The operation of anterior resection has been described so often in the past few years that it is unnecessary at this time to go into all the details. Figures 1 to 7 depict the essential features of the procedure. A few points call for clarification and emphasis. We ligate the superior hemorrhoidal and last sigmoidal vessels at the same time, thus removing a somewhat longer segment of lower sigmoid and assuring the extirpation of all lymph nodes in the lower mesosigmoid. The rectum is bluntly dissected from the hollow of the sacrum and lateral pelvic walls almost to the tip of the coccyx in the same manner as this step is carried out for abdominoperineal resection. The ureter is isolated and retracted laterally on each side and lateral and anterior peritoneal flaps are carefully prepared. For cancers at the rectosigmoid, it is not necessary to divide the middle hemorrhoidal vessels because a wide enough resection can be accomplished without this maneuver. For growths below the rectosigmoid, if the operation of anterior resection is carried out (and we believe that it should not be employed in the vast majority of instances), it will become necessary to ligate the rectal stalks and their contained middle hemorrhoidal vessels in order to obtain sufficient mobilization of the lower rectum for a wide resection. As a result of our experience with this procedure, we have come to believe that the point of division below the lower edge of the tumor should be *not less* than 2 to 3 inches. We say this because we do not believe one can carry out a radical operation for cancer unless a wide margin of normal rectal wall with its surrounding fat and cellular tissue is excised both proximal and distal to the growth. Unless this is done, one cannot be sure that he is removing possible submucosal or mural lymphatic spread distal to the tumor. Wangensteen suggests that an area 3 centimeters distal to the tumor edge should be sufficient to assure radical extirpation. We do not think that this is enough. This one feature of wide *distal* excision constitutes, we believe, the major difficulty with the operation of anterior resection for growths below the rectosigmoid in the rectal ampulla as evidenced by the high incidence of local recurrence at the suture line in the follow-up period. Our figures bear out this contention.

As a result of our operative experience, we believe that the so-called dangerous area of Sudek is grossly exaggerated. Even with ligation of the middle hemorrhoidal vessels, we have never been perturbed by paucity of blood supply of the distal rectal segment. Because of the absence of a peritoneal layer posteriorly and laterally, healing of the anastomosis at these sites takes place by granulation and secondary intention. Temporary fecal leaks have occurred in approximately 5 per cent of our cases. We attribute this low incidence to: (1) thorough hemostasis, (2) open anastomosis without clamps which permits an accurate mucosal suture, (3) the avoidance of too many sutures, thus minimizing the possibility of interference of local blood supply, and (4) the routine employment of some type of proximal decompression of the colon.

The placing of the sutures at the site of anastomosis is carried out with great care. Fine chromic catgut is used for the mucosal stitch and interrupted fine silk is employed for the second outer layer. On the average, 12 or 14 sutures are all that should be necessary for the outer layer. Each one is placed accurately and tied without tension. We are of the opinion that the use of too many sutures in this type of anastomosis is a major reason for local interference of blood supply and subsequent leakage. We have constructed the new pelvic diaphragm of peritoneum above the anastomosis and have drained the retrorectal pelvic space through the lower angle of the lower midline abdominal incision.

Up to a year ago, we routinely employed proximal decompression by a glass rod transverse colostomy carried out through a small upper right rectus incision at the same sitting. These colostomies were closed approximately 16 to 21 days later after patency and firm

healing of the anastomosis were demonstrated by irrigations from above and below. In the past year, we have been employing complementary tube cecostomy instead, primarily for gas decompression of the colon. We believe that proximal decompression makes for a smoother convalescence and more rapid healing at the suture line.

ANALYSIS OF CASES

The 163 cases comprising the group reported in this paper include 128 private patients of the authors and 35 ward patients on the service of the senior author. We believe it would be of interest to separate the series into 2 groups for analysis and finally combine them in order to arrive at definite conclusions. The private cases of the authors comprise a group of 128. In this group there were 6 postoperative deaths, a mortality of 4.6 per cent. In order thoroughly to appraise the operation for various levels of the rectum, we have started at 3 inches from the anus to indicate the lower level of each tumor as demonstrated on sigmoidoscopy. Each level of 1 inch will be arbitrarily separately grouped.

In the 122 survivors of the group under discussion, there were 13 patients with tumors in the 3 to 4 inch level. Only 1 specimen showed lymph node involvement and this node was 1 inch below the lower level of the tumor. In this case a local recurrence was noted 6 months later resulting in death. Another specimen presented penetration of the tumor to the perirectal fat. This patient developed a recurrence at the suture line 15 months later and subsequently succumbed. A third patient without penetration or node involvement developed a recurrence at the suture line and died later. The fourth case in this subgroup is of considerable significance. Three and one-half years after operation a small recurrence in the mucosa was demonstrated at the posterior suture line. It was possible to carry out an abdominoperineal resection 4 months ago. No penetration or node involvement was evident in the specimen. The ability to carry out a secondary resection in those individuals in whom recurrences of cancer have developed after anterior resection is decidedly rare in our experience. Almost invariably the secondary

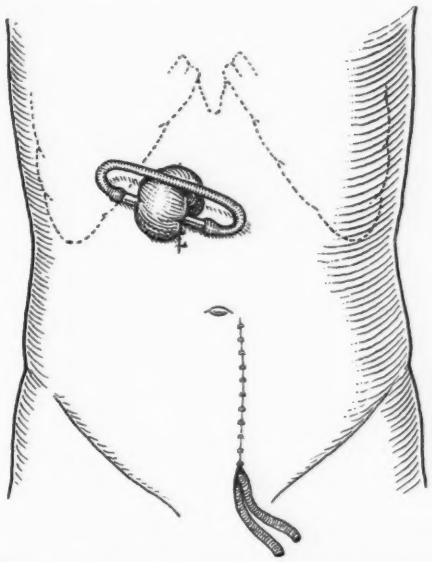

Fig. 7. Proximal decompressive transverse colostomy. During past year, we have been using a tube cecostomy instead.

explorations have revealed locally inoperable conditions. The remaining 9 patients are alive and apparently free from recurrence: 1 after 3 months, 2 after 2 years, 1 after 2½ years, 3 after 3 years, and 2 after 3½ years. In this group the local recurrence rate is 30 per cent (Table I).

There were 14 patients with growths in the 4 to 5 inch level. Three had lymph node involvement and 1 showed spread to the perirectal fat. Two developed recurrence at the suture line in 10 months and subsequently died, and 1 died of recurrence in the pelvis after 6 months. Three other patients developed local recurrence at the anastomosis after 6, 12, and 21 months respectively, and died. One patient died 3½ years later of hepatic and pulmonary metastases. The remaining 6 patients are alive and well: 2 for 3 years, 3 for 2½ years, and 1 at 9 months after operation. In this group the rate of recurrence at the suture line was 35.7 per cent, and in the pelvis, 7.1 per cent.

There were 29 instances of growths at the 5 to 6 inch level. Two had palliative resections inasmuch as hepatic metastases were

TABLE I.—DATA ON 122 SURVIVORS OF 128 PRIVATE PATIENTS

Level of growth	Total No.	With lymph node or perirectal spread			Without node spread			Palliative resection	Recurrence rate		Combined percentage
		Recurrence		Well	Recurrence		Well		Suture line per cent	Pelvis per cent	
		Suture line	Pelvis		Suture line	Pelvis					
3 to 4 inches	13	1	0	0	3	0	9		30	0	
4 to 5 inches	14	2	1	1	3	0	6	1 patient died of hepatic metastases	35.7	7.1	42.8
5 to 6 inches	29	2	2	2	1	1	17	2	10.3	10.3	20.6
							2 died hepatic metastases				
6 to 8 inches or rectosigmoid	66	1	1	8	1	0	44	5	3.3	1.6	4.9
				1 died hepatic metastases			1 died coronary 1 year later				
				1 died cerebral accident			1 died sudden 2 mo.				
							2 died carcinosis				

noted at the time of operation. Six patients presented lymph node spread. Of these, 2 died 6 and 10 months later of a recurrence in the pelvis, 2 developed recurrences at the suture line 17 and 14 months postoperatively, 1 is well after 9 months, and 1 has a stricture at the suture line. Inasmuch as the latter is one of 3 instances of local stricture in this series we suspect local recurrence although numerous biopsies have been reported negative. Further observation is obviously necessary. In the group of 21 patients without node spread, 2 died of hepatic metastases 15 and 16 months later. One developed a recurrence at the suture line at 12 months, and another a recurrence in the pelvis at 14 months. The remaining 17 patients are alive and apparently well: 36 to 42 months in 2 cases; 30 to 36 months in 3; 24 to 30 months in 5; 16 months, 9, 8, and 7 months in 1 case; and 6 months in 3 cases. The recurrence rate at the suture line is 10.3 per cent. The local recurrence rate in the pelvis is the same.

There were 66 cases of tumors at the 6 to 8 inch level or what we take to represent the rectosigmoid area as demonstrated at the operating table. Fourteen of these specimens disclosed node involvement. Two of the latter also presented local peritoneal implants and the patients died of recurrence in the pelvis 4 months and 1 year later. Another died of hepatic metastases after 10 months. Of the remaining 11, one died of recurrence in the pelvis 3 months later, 1 with colloid cancer developed a recurrence at the suture line 1 year later, 1 died of a cerebral accident 3 years later without evidence of recurrence, and the rest are apparently well 3 years, 2 years, 1½ years, 2 at 1 year, 7 months, 6 months, and 4 months after operation. In the remaining 52 patients without demonstrable node involvement, local factors influenced survival in a few instances. One patient died suddenly at home 2 months after operation. Another patient with peritoneal implants in the pelvic peritoneum died of recurrence in the pelvis 6 months later. This case must be classed as a palliative resection. A patient who presented a pelvic abscess at the time of resection died of recurrence in the pelvis 3 years later. One patient with implants on the surface of the lower mesocolon and involvement of an adherent loop of ileum which was resected died of a recurrence at the suture line and in the

TABLE II.—DATA ON 29 SURVIVORS OF 35 WARD PATIENTS

Level of growth	Total No.	With lymph node or perirectal spread			Without node spread			Palliative resection	Recurrence rate		Combined percentage
		Recurrence		Well	Recurrence		Well				
		Suture line	Pelvis		Suture line	Pelvis			Suture line per cent	Pelvis per cent	
3 to 4 inches	7	1	1	1	0	1	1 1 died coronary	1	20	40	60
4 to 5 inches	5	2	0	1 died carcin.	0	0	2		40	0	
5 to 6 inches	2	0	0		0	0	2		0	0	
6 to 8 inches or rectosigmoid	15	0	0	3	1	0	8 1 died lumbar gutter rec.	2	8.3	0	

pelvis 10 months later. One patient died of coronary thrombosis 1 year after operation. The final patient developed a recurrence at the suture line 1 year later. After another resection was accomplished a second recurrence developed after 5 months resulting in death. Two died of carcinosis after 10 and 11 months. The remaining 44 patients are alive and apparently well for varying periods: viz., 1 at 5 years, 1 at 4 years, 6 at 3 to 4 years, 7 at 2 to 3 years, 8 at 1 to 2 years, and 21 under 1 year. In this group there were 2 instances of double carcinoma. In 1 case, the lesions were at the rectosigmoid and midrectum and in the other at the rectosigmoid and descending colon. The former patient is well 2 years and the latter 3 years after operation. If 5 cases are excluded from the entire group because they were really palliative resections because of irremovable local spread of disease, 61 patients remain for critical study. In this group there were 2 recurrences at the suture line and 1 recurrence in the pelvis. Three patients died of other causes, 1 too soon after operation to be included. The incidence of recurrence at the suture line is 2 in 60 patients or 3.3 per cent. If the recurrence rate in the pelvis of 1.6 per cent is included, the percentage is 4.9.

The ward series comprises 35 patients operated upon by members of the resident and attending staff. There were 6 postoperative deaths, a mortality of 17 per cent in this group. The causes of death were: 1 of uremia, 2 of pulmonary embolism, 2 of sepsis, and 1 of dehiscence of the suture line with extensive bronchopneumonia. Postmortem examinations were obtained in all except the first mentioned. Of the 29 survivors, there were 7 cases in the 3 to 4 inch area. Three of these showed lymph node involvement. One patient died of recurrence in the pelvis 6 months later, 1 developed recurrence at the suture line in 5 months and the third, with a colloid growth, is alive and locally free of recurrence 3 months later, too short a period. In the 4 without node spread, 1 had liver metastases and a palliative resection was done. A second patient died of coronary thrombosis 5 months later. The third patient died 3 years later of recurrence in the pelvis. The fourth is well after 13 months. If we exclude the case of palliative resection and of coronary thrombosis, there was 1 recurrence at the suture line, an incidence of 20 per cent, and 2 recurrences in the pelvis or 40 per cent, with a combined recurrence rate of 60 per cent (Table II).

In the group in the 4 to 5 inch area, there were 5 cases, 3 of them exhibiting node involvement. Of the latter, 1 patient died of recurrence at the suture line 2½ years later, in 1 recurrence at the suture line developed after 3 months, and the third died of carcinomatosis 6 months later. The 2 patients without node spread are alive and apparently well after 2 years and 4½ years, respectively. The latter had a double carcinoma, the second

TABLE III.—DATA ON 151 SURVIVORS OF COMBINED GROUPS

Level of growth	Total No.	With lymph node or perirectal spread			Without node spread			Palliative resection	Recurrence rate		Combined percentage
		Recurrence		Well	Recurrence		Well		Suture line per cent	Pelvis per cent	
		Suture line	Pelvis		Suture line	Pelvis					
3 to 4 inches	20	2	1	1	3	1	10 1 died coronary	1	27.3	10.5	37.8
4 to 5 inches	19	4	1	1 1 died carcinosis	3	0	8	1 patient died of hepatic metastases	41	12	53
5 to 6 inches	31	2	2	2	1	1	19 2 others died hepatic metastases	2	10	10	20
6 to 8 inches or rectosigmoid	81	1	1	11 1 died hepatic metastases 1 died 1 yr. cerebral accident	2	0	52 1 died coronary 2 died carcinoma 1 died sudden 1 died lumbar rec.	7	4.4	1.4	5.8

of which was located in the sigmoid colon. In this group the recurrence rate at the suture line is 40 per cent.

In the 5 to 6 inch area, there were 2 cases. Neither patient had node spread and 1 had another carcinoma at the splenic flexure necessitating another operation. Both are well after 2½ and 4½ years, respectively.

In the group at the site of the rectosigmoid, there are 15 cases for study. There was only 1 instance of node spread and this patient is alive and well 1 year after. Of the remainder, 2 cases must be classed as palliative resections because of the presence of local peritoneal implants at operation and these patients died within a year. A third patient had another carcinoma in the ascending colon requiring a second procedure. Death occurred 5 months later of recurrence in a lumbar gutter. There was only 1 instance of recurrence at the suture line, noted 13 months after operation. The remaining 10 patients are alive and apparently well: 1 after 4½ years; 1 after 4 years; 2 after 3 years; 1 after 2½ years; 1 after 1½ years; 2 at 1 year; and 2 under 1 year. Excluding the palliative resections and the recurrence in the lumbar gutter, the recurrence rate at the suture line is 10 per cent.

Combining the 2 groups, there is a total of 163 patients with 12 deaths or an operative mortality of 7.2 per cent. Of the 151 survivors, 20 come within the 3 to 4 inch level. In this group, the recurrence rate at the suture line was 27.3 per cent and the recurrence incidence in the pelvis was 10.5 per cent, or a combined percentage of 37.8. It must be remembered that in the great majority of these latter patients, anterior resection was done because the rectal tumor was small and therefore seemed suitable for an operative procedure to preserve the sphincters. In the group of 19 located at the 4 to 5 inch level, the recurrence rate at the suture line was 41 per cent while the incidence of recurrence in the pelvis was 12. As the distance from the anus increases, the local recurrence rates fall markedly. In the group of 31 patients with tumors located at 5 to 6 inches, the recurrence in-

cidences at the suture line and in the pelvis were similar—10 per cent. The largest group of the series comprises the tumors located at the 6 to 8 inch level, or what we take to represent the rectosigmoid area. In this group of 81 patients, the recurrence rate at the suture line was 4.4 per cent as opposed to a recurrence percentage of 1.4 in the pelvis (Table III).

DISCUSSION

In our consideration of the problem of cancer of the rectum with respect to the employment of sphincter-saving operations, we purposely and arbitrarily separated the organ into various levels starting from 3 inches from the anal margin. For cancers below the 3 inch level, there is ample reliable statistical evidence to support the view that any operation short of the abdominoperineal resection cannot be considered radical enough to meet the requirements of good cancer surgery. As pointed out so well by David and Gilchrist, this area of the rectum is intimately connected with important muscular and fascial attachments as well as contiguous viscera so that it must be considered in a different light from segments of the organ at higher levels. It must also be emphasized that this distal portion of the rectum is located below the peritoneal pouch of Douglas or below the reflection of peritoneum onto the bladder in the male and vagina in the female.

Lacking other absolute criteria which would aid the surgeon in choosing between a sphincter-saving operation and an abdominoperineal resection, we decided on the exact location of the tumor as the deciding factor, all other considerations being equal, and initiated this study on that basis. This study has shown that neither the Dukes classification, nor the Broders histological differentiation into grades nor the question of lymph node spread can be used as absolute criteria at the operating table. It seems to us that this study has conclusively shown that sphincter-saving operations should rarely, if ever, be employed for cancers of the rectum below the level of 5 inches from the anal margin because of the inability of the surgeon to excise sufficient rectum distal to the tumor to meet the requirements of radicability demanded in the performance of a good cancer operation. On the other hand, this study has also shown that it is not necessary to perform an abdominoperineal resection for all cancers of the rectosigmoid and that it is possible to carry out as thorough a cancer operation with preservation of the sphincters and with a negligible incidence of local recurrence.

The criticism may be made that many of our patients have not been followed long enough to warrant drawing definite conclusions, especially in the group with lesions below the rectosigmoid. It seems clear to us that, with longer follow-up observations in the group now apparently well, there will be a steady increase in the number of local recurrences. We do not believe that this will apply to the group with lesions of the rectosigmoid, first, because of the anatomy of the region and, second, because the surgeon is able to carry out a more radical operation for tumors in this location than for growths below this level.

The patients in the series herewith reported have been followed most carefully. They were seen at regular intervals and appraised thoroughly by every method of examination at our disposal. The facts elicited on the basis of a personal follow-up study have, of course, greater significance than those obtained by other means. The data accumulated in this study have charted the way for us in the surgical therapy of cancer of the rectum and rectosigmoid. We have given up the operation of anterior resection, except under very unusual circumstances, in the treatment of cancer of the rectum proper and employ it, when local conditions permit, for cancer of the rectosigmoid. It is hoped that others who have employed the operation of anterior resection will report their results in the same way that we have, so that a clear picture of the problem may evolve on the basis of a much larger group of patients than was reported in this paper.

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HYPERTROPHY OF PYLORIC MUSCLE IN ADULT

Experiences with Conservative and Radical Surgical Treatment

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HYPERTROPHY of the pyloric muscle, rarely observed in the adult, is a condition in which the circular muscle of the pylorus is grossly hypertrophied producing symptoms of obstruction. It may or may not be associated with gastrointestinal pathology. On the other hand, hypertrophy of the pyloric muscle is not infrequently seen in the infant, more commonly among first-born males. In a 4 year survey of congenital defects in the newborn in the city of Philadelphia (19), 275 cases were studied; of these, 35 had gastrointestinal tract deformities, and of this group 20 had pyloric stenosis. In the infant this condition is usually associated with no other gastrointestinal disease. The hypertrophied pyloric muscle forms a firm, almost cartilaginous mass producing variable degrees of obstruction. Usually, if untreated, the condition becomes progressively more complete and the symptoms more severe. The stomach proximal to the obstruction dilates and secretes an excess of mucus which frequently forms a plug in the pylorus to complete the obstruction. The normal infant pylorus (26) varies in length from 1.0 centimeter to 1.5 centimeters; the hypertrophied pylorus varies from 1.5 centimeters to 3.0 centimeters. The normal infant pylorus varies in width from 0.05 centimeter to 0.25 centimeter; the hypertrophied varies from 0.3 centimeter to 0.7 centimeter. Microscopically, the changes from normal are limited to the submucosa and the circular muscle; the submucosa is usually thickened by collections of edema fluid; the circular muscle is hypertrophied with no concomitant increase in the thickness of the longitudinal muscle or the connective tissue coat. In the adult form of hypertrophy 2 distinct types are seen: (1) idiopathic; (2) concomitant. In the idiopathic type, no other demonstrable pathology is found within the gastrointestinal tract; in the concomitant type, other pathology is found, such as duodenal or gastric ulcer, or chronic gastritis with superficial ulceration. In either case the circular muscle is hypertrophied just as in the infantile form with elongation and narrowing of the pyloric orifice.

It is necessary to recall the anatomy of the pylorus to understand better this localized pathologic entity. The arrangement of the circular muscle of the pylorus is such that in over 96 per cent of subjects there is a complete break (8) between the circular muscle of the pylorus and the circular muscle of the duodenum. The longitudinal muscle, however, is more variable; about 50 per cent of the longitudinal fibers interdigitate with the circular muscle to form the dilator muscle of the pylorus, while less than 25 per cent continue into the duodenum. Thus, the pylorus is a complete sphincter with both a dilator and a constrictor muscle. The bulk of the circular muscle is four to five times greater than that of the longitudinal muscle. The circular muscle has connective tissue septa which run perpendicular to the long axis of the pylorus; these divide the circular muscle into numerous closely associated units. Cross sections made through the pylorus at different levels reveal variations in the thickness of the circular muscle because of these septa. Continuity between the submucosa and the circular muscle is established via these connective tissue septa; this undoubtedly accounts for the submucosal edema in hypertrophy of the pyloric muscle. On the other hand, the connective tissue septa rarely ever penetrate the longitudinal muscle; this may explain the lack of edema in this layer in hypertrophy of the pylorus. Horton (9) concluded from his detailed histologic

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studies that the complete separation of the circular muscle of the pylorus from the circular muscle of the duodenum had physiologic significance in that this separation causes a block in the antral wave as it reaches the pylorus. He felt that the changes in tonus of the duodenal musculature were due to a spread of some influence along the myenteric plexus or along the narrow bridge of longitudinal muscle connecting the duodenum and the stomach.

Credit for first recognizing hypertrophy of the pyloric muscle has been given to Fabricius Hildanus (22) for his "Observanti Singularis de Obstructori Pylori," unearthed by Kellet. In 1675 Wolfgang Helfer, noting the above reference, wrote that it was so rare that he himself had never seen a case. Early reports were made by Blair in 1717, Weber in 1758 and Armstrong in 1771. In 1788 Hezekiah Beardsley reported hypertrophic pyloric stenosis, found at autopsy in a 5 year old boy, to the New Haven Medical Society. In 1835 Jean Cruveilhier, reporting the case of a 72 year old female who had vomited all her life, described hypertrophy of the pyloric muscle found at postmortem examination. A typical case was reported by Williams in 1841. Siemon-Daworsky reported 10 adult cases in 1842. In 1879 Landerer applied the term "congenital pyloric stenosis" to the condition. In 1885 Maier wrote of his findings in 31 cases in the adult, studied at postmortem. Hirschsprung wrote his classic description of the condition in 1888. One year earlier, he reported postmortem findings in 2 cases before the German Pediatric Society. In 1893, Tilger reviewed the German, French, and English literature and collected 23 cases, adding 1 of his own proved at postmortem examination. Attention was first called to the palpable tumor by Finkelstein in 1896.

Theories concerning etiology have never satisfactorily explained all the clinical cases that have been reported. For both the adult and infantile forms, it has been suggested that they may represent a persistence of the relatively thick pylorus normally present at the fifth to sixth month of embryologic development (9). This view holds that the symptoms after birth and through maturity may be mild enough to escape detection until the obstruction becomes more complete in adult life, or that the symptoms demanded medical or surgical therapy shortly after birth. Morton speculates that either the varying degrees of hypertonicity and spasticity seen in infancy may carry over into childhood and adult life or that the process may arise *de novo* in an entirely normal person. Crohn too felt that the adult hypertrophy of the pylorus represents a carry-over from the infantile form and doubted that many will be seen today in adult life because of earlier intervention and successful therapy by the Fredet-Ramstedt operation. Oliver felt that the etiologic factor for both the infantile and adult forms was the same because "we are dealing with the same condition." Brown noted that once established, the condition is permanent. Wallstein proved that in those patients treated medically and those treated by gastroenterostomy the tumor remained the same.

Martin and Burden believed that infantile hypertrophy, whatever its relation to the adult form, may result from intermittent clonic spasm, which begins in intrauterine life, and may be caused either by a preponderance of sympathetic influences or by impaired or tardy development of vagal inhibition. An excess of adrenalin secretion, which is a powerful stimulus to the sphincter, may be a factor. They felt that with reference to a relationship between dysfunction of the pyloric sphincter and peptic ulcer, it is significant that infantile hypertrophy and peptic ulcer occur with much greater frequency in males than females. Bendix and Necheles suggest that in intrauterine life the amniotic fluid with its meconium, cell detritus and possibly hair may irritate the sphincter so that edema, spasm and enlargement result. Thus local trauma plus autonomic imbalance may be the causative factor.

McClure believes that hypertrophy may be due to long standing spasticity of the pyloric muscle. In his case reports, he noted "nervousness alone is capable of producing a spasticity of the pyloric muscle which if long continued may in turn cause hypertrophy of the spastic tissue." Katz suggested that since smooth muscle hypertrophies with dilatation,

an imbalance between the circular and longitudinal muscle tone may lead to dilatation and later hypertrophy. He discounts spasm as a factor because of the relatively common finding of pylorospasm without hypertrophy. He recognized, too, that a subclinical form of hypertrophy may exist from birth. Vorhaus, unwilling to speculate on the etiology, calls it an enigma in adult life. Freeman makes an interesting observation while discounting spasm, namely, that spasm occurs in many muscles of the intestinal tract, i.e.; anus, cardia of stomach—without hypertrophy. He suggests that hypertrophy may represent a throwback to ancestral types, observing that in the graminivorous bird, the gizzard is located in the same spot as the pylorus; in the colored ant eater, the outlet of the stomach is occupied by a heavy muscle tumor in the same situation as the tumor in pyloric muscle hypertrophy.

Individual case histories are extremely variable with the initial symptoms caused by hypertrophy often going unrecognized. Vorhaus believes that hypertrophy of the pyloric muscle in the adult can be divided into 2 categories: (a) those with signs and symptoms of very short duration, with no other gastrointestinal pathology and (b) those with signs and symptoms from childhood. Bochus divides them into 3 groups: (a) those with signs and symptoms from childhood, (b) those with atypical ulcer symptoms of long duration beginning in adult life, and (c) those who quickly develop signs and symptoms of pyloric obstruction in middle or late life. Judd and Thompson found that symptoms varied from 1 to 42 years and averaged 10½ years. Vomiting was the most common symptom. Weight loss and constipation were the next most common. Patients have a variety of complaints; soreness and fulness in the epigastrium, lump in the stomach, stomach fills quickly, frequent eructations, epigastric heaviness, dyspepsia, postprandial pain and night regurgitation of acid material. Objective findings noted most frequently were weight loss and dilation of the stomach. Occasionally a palpable upper abdominal tumor was found.

In a review of 60,000 roentgen examinations of the stomach, Kirklin and Harris found 81 cases of hypertrophy of the pylorus which were verified at operation. In all, they found elongation of the pyloric ring with crescentic indentation of the bulbar base. Other associated findings were hyperperistalsis, gastric dilatation and retention. One case was diagnosed preoperatively as hypertrophy of the pylorus. Stone and Ruggles studied a group of abnormalities found in the pylorus and prepyloric region and concluded that practically no type of deformity was characteristic of a definite disease or lesion. They felt that hypertrophy of the pylorus had 2 suggestive features: (a) decreased diameter of the orifice and failure to open, (b) elongation of the pylorus with an immediate prepyloric deformity. On the other hand, Berk (24) believes that the roentgenogram is not diagnostic since malignant infiltration may produce a concentric narrowing of the distal portion of the stomach similar to hypertrophy. Gastroscopy is of aid in ruling out ulceration and malignancy. Papanicoloau study of aspirations would reveal no diagnostic changes. Acidity is of no diagnostic importance, though many are either hypochlorhydric or achlorhydric. In the final analysis, diagnosis must rest on suggestive roentgen findings and surgical exploration.

Surgical therapy for the infantile form is fairly well established in this country, though antispasmodics are still used with success in Denmark (2). The first attempt at surgical therapy was made in 1882 by Loreta of Bolgne (22). His procedure consisted of digital dilatation of the pylorus. Heinecke in 1886 and Mikulicz in 1887 tried pylorotomy. In 1893 Cordua advocated jejunostomy. Stein in Germany and Meyer in New York both suggested gastroenterostomy in 1898. In 1905 Scudder collected 60 cases in which various methods of treatment were used and he found a mortality of 45 per cent. In 1906 Nicoll suggested a pyloroplasty using a V shaped submucosal incision. In 1908 Fredet proposed longitudinal division of the sphincter with a transverse closure. Ramstedt found in 1912 that the transverse closure was of no added value and simply divided the muscle longitudinally. Since then, the extramucosal, longitudinal division of the sphincter has been called the Fredet-Ramstedt method. It is now employed with a mortality of less than 0.5 per cent. In

Fig. 1. Dilated stomach showing narrowing and lengthening of pylorus. Note functioning gastroenterostomy.

treating the adult form, a survey of reported cases reveals that therapy has varied from simple dilatation of the sphincter to pyloroplasty, gastroenterostomy and subtotal gastrectomy.

CASE PRESENTATIONS

Idiopathic Type

CASE 1. A 55 year old single white maid was admitted to St. Vincent Hospital on November 3, 1948, complaining of dull epigastric pain, fulness, anorexia, and diarrhea. The patient stated that following an operation in 1942 she felt well and enjoyed a good appetite up until approximately 8 months prior to admission.

During childhood the patient was a state ward. She remembered little of her early life. She stated that the only illness she had had in adolescence was an attack of appendicitis which subsided and required no operation. In 1942, at the age of 49, she was hospitalized for epigastric pain and backache. Her epigastric distress was aggravated by solid foods, so she limited her diet to liquids. She felt that when present the pain was increased rather than relieved by food in any form. She experienced considerable belching but no nausea and no vomiting. She lost approximately 21 pounds in weight. Gastrointestinal studies done at that time showed "an extensive filling defect involving the distal third of the stomach, producing obstruction as there is a substantial 24 hour residue. The character of the deformity is typical of new growth. The x-ray would indicate that there is some infiltration of the growth along the lesser curvature beyond the midline of the stomach. It is of course possible that we are dealing with ulcer with a very extensive fibrosis." (These x-rays are not now available for re-evaluation.)

The dictated operative note reads, "The stomach was found to be slightly larger than normal, the pyloric sphincter was very much contracted and indurated, although there was no scar of an ulcer visible. The pyloric sphincter would not admit the finger. Because of the nature of the pylorus, a posterior gastroenterostomy was decided upon. When the stomach was opened a finger was placed inside the fundus for digital examination of the pylorus; the tip of the finger could not be forced through the pyloric sphincter." The gastroenterostomy functioned well and the patient had 5 years of freedom from discomfort.

In the present illness she first noted epigastric fulness, a progressive increase in epigastric distress and loss of appetite. In the 8 months of her illness she became morose and depressed, fatigued easily, and lost 30 pounds in weight. Immediately after eating, she had the urge to defecate; the consequent bowel movement was usually large and soft to loose in consistency. During this 8 month period she was living in the household of a physician and was repeatedly examined during the severest episodes of distress. At no time was hospitalization considered necessary. Roentgen examination done in March revealed a narrowed pyloric antrum through which no barium could be forced, a slowly emptying gastroenterostomy and diverticulosis of the colon. During the examination she complained of no tenderness over the stoma of the gastroenterostomy and no ulcer could be seen. In May, a gastroscopy was done, at which time the pylorus could not be visualized but a marginal ulcer was said to be observed on the posterior inferior margin of the stoma. Surgery was advised.

She showed evidences of weight loss, particularly about the face and neck. The abdomen was moderately obese; no distention, mass, tenderness or spasm was found. Gastric analysis revealed 2 plus blood, alkaline reaction, positive lactic acid and no free hydrochloric acid. The gastrointestinal films showed the outline of the stomach smooth with active peristalsis; the gastroenterostomy stoma appeared adequate and emptied barium readily. No ulcerations were demonstrable either in the stomach or the enteroenterostomy stoma. Very little barium passed into the antrum beyond the stoma of the gastroenterostomy. "The appearance of this segment is somewhat disturbing inasmuch as it appears narrowed and fixed in outline" (Fig. 1). The radiologist interpreted this as due to disuse. Surgical exploration was advised and accepted.

At operation there was no evidence of previous ulcer—no stippling and no scar. The gastroenterostomy stoma measured 3 fingers' breadth in width. The pylorus was very thick and hard, measuring approximately 2.5 centimeters in diameter; under stimulation it did not relax and did not permit approximation of fingers through the lumen. The gastroenterostomy was taken down; the mucosal surfaces of the stomach and jejunum were carefully inspected and no ulceration or scarring was found. The gastric mucosa was hypertrophied, no superficial ulcers were seen. Digital exploration of the pylorus from within revealed a firmly stenosed opening which persisted despite attempts at dilatation. A Billroth I type of pylorectomy was performed after the stomas in the stomach and jejunum were closed.

The gross specimen consisted of a portion of stomach measuring 6.0 by 5.0 by 1.5 centimeters. The mucosa was thick and smooth. The muscularis was definitely thickened, varying from 0.8 to 1.8 centimeters in thickness. The serosa was thin and smooth.

Microscopic examination revealed the following: "The muscularis showed large bands of smooth muscle. Occasionally in the interstitial fibrous tissue there were scattered chronic inflammatory cells. The mucosa was infiltrated with lymphocytes, occasional plasma cells and a moderate number of diffusely distributed eosinophiles" (Fig. 2.).

Follow-up report on the patient finds her in excellent spirits with her appetite, weight, and energy regained. Gastric analysis done 6 weeks after operation showed no residue and an achlorhydria.

CASE 2. A 27 year old religious female was admitted to St. Vincent Hospital August 6, 1930, complaining of epigastric distress, burning, fatigue, intolerance to fried and fatty foods, gaseous eructations, and constipation. The patient stated that she noted seasonal variations in the frequency of symptoms with onset at age of 18 years. For the past 2 years, constipation was severe enough to require frequent catharsis.

Past history, physical examination and routine laboratory studies added nothing of significance. Barium meal studies showed a marked constriction of the pylorus, unrelieved by amyl nitrate, no antral dilatation and a tiny duodenal bulb. There was a 6 hour residue of approximately one-third of the barium. Fluoroscopic studies revealed small amounts of barium passing into the duodenum with each antral wave. Roentgen interpretation was "obstructing lesion either at the pylorus or duodenal bulb." Operation was advised and accepted.

At operation the pyloric muscle was found to be markedly hypertrophied and the narrowed orifice would hardly admit the tip of the small finger. No evidence was found to indicate ulcer or other disease. A Balfour type of pyloroplasty, removing three-fourths of the sphincter, was performed.

Fig. 2. Note the edematous mucosa and the marked hypertrophy of the circular muscle. The muscle measures 1.8 centimeters at its thickest point, which is over 3 times the thickness of the normal adult pyloric muscle (0.5 cm.). Coin shown measures 2.2 centimeters.

The gross specimen consisted of a "diamond shaped piece including part of the pylorus. The sphincter was hypertrophied 4 times. On the duodenal side just beside was an indurated area 0.5 centimeter in diameter. No ulcerations were noted." Measurements recorded indicate that the pyloric muscle measured 3.0 centimeters in thickness.

Patient had only temporary relief from her symptoms. Later, recurrence of discomfort was reported from a Canadian Hospital, where a gastroenterostomy was performed. She suffered a reactivation of quiescent pulmonary tuberculosis from which she later died.

Concomitant Type

CASE 3. A 47 year old white male was admitted to St. Vincent Hospital October 27, 1936, complaining of epigastric pain, belching, sour eructations, vomiting of solid food and weight loss of approximately 15 pounds in 3 months. Previous history was essentially negative. Vomitus was positive for blood; gastric analysis revealed blood on 2 specimens and a high free and total hydrochloric acid.

Barium meal study demonstrated a long period of pylorospasm which could be relieved with 20 milligrams benzedrine sulfate. The antrum was narrowed ½ inch proximal to the pylorus to an orifice measuring approximately ¼ inch in diameter with smooth, fixed outlines. At 6 hours, there was a residue of approximately one-quarter of the barium. At 24 hours, the stomach was empty. Two small ulcers were found in the duodenum and 2 small projections (? ulcers) on the lesser curvature of the stomach. Radiologist's interpretation was, "Narrowing at antrum may be secondary to ulcers, but malignancy and a luetic lesion cannot be ruled out." Operation was advised and accepted.

Fig. 3. Note marked thickening of the pyloric musculature (2.0 cm.). Note also hypertrophy of the gastric rugae with associated gastritis.

At operation, the lesser curvature was found to be indurated and stippled, the pylorus was elongated and hypertrophied, extending back onto the antrum for a distance of approximately 1 inch; the thickening ended abruptly at the duodenum. To the operator it suggested an intramural tumor. In addition, a small healed duodenal lesion was found. A subtotal gastrectomy with posterior Polya-Mayo type of gastrojejunostomy was performed.

The gross specimen showed a smooth mucosa with several small areas of ulceration which did not appear to extend through the mucous membrane. The muscle in the wall of the stomach near the pylorus was enormously thickened, measuring more than 2 centimeters from mucosa to serosa. This thickening was well localized and was not diffuse throughout the specimen (Fig. 3).

Pathologic diagnoses: (1) multiple superficial gastric ulcers: (2) hypertrophy, marked, of gastric musculature (pyloric end).

Follow-up: The patient's subsequent clinical course was satisfactory.

Each of these 3 patients exhibited hypertrophy of the pyloric muscles. In the third patient only was associated pathological conditions found. The first 2 cases present evidence of failure of conservative surgical procedures (pyloroplasty, gastroenterostomy). Our experience with these 3 cases indicates that resection, preferably with Billroth I type of reconstruction, is the surgical treatment of choice.

DISCUSSION

Our experience offers no new information on the enigma of hypertrophy of the pyloric muscle in the adult. That this is a distinct clinical entity cannot be doubted, and it matters little that 2 types can be distinguished, for the therapy is the same and the results of the therapy uniformly good. The fact that the pathology in the adult form of hypertrophy is the same as in the infant seems to lend weight to the theory that it represents a subclinical variant of the congenital form. Subsequent examination of the pyloric muscle that had been primarily by-passed by a gastroenterostomy, and postmortem examinations of the untreated pylorus in congenital hypertrophy of the pylorus have revealed no change in the pyloric tumor. In our experience both idiopathic forms were in women. In the cases surveyed there were 130 males to 30 females. Those who believe that autonomic imbalance in some way favors the development of the pyloric muscle hypertrophy feel that this sex incidence, noted in both the infantile form and the adult form, is significant. The high incidence of psychoneurotic tendencies in children treated for congenital hypertrophy and similar findings in the adult with hypertrophy are viewed with interest and thought to be indicative again of autonomic imbalance; though to be fair to the patients suffering from this entity, symptoms are not often interpreted early and diagnoses are more often delayed than entertained. This fact does, however, raise the question of which comes first, the psychic overlay or hypertrophy.

With due regard for those who feel that spasm is an etiologic factor, it seems improbable that we should see peptic ulcer so frequently in the 20th century and pyloric hypertrophy so infrequently. In 1904 Maylord reported 7 cases, all females, in which the pyloric orifice was narrowed but the pyloric muscle was not hypertrophied. Associated with the narrowing, he found considerable mucus and secondary gastritis. In view of this it would seem logical that gastritis can accompany or follow stenosis but unlikely that true hypertrophy would accompany or follow ulcer or gastritis. At the present time, it appears that no one theory has satisfactorily explained the presence of hypertrophy of the pylorus in the adult. Speculation on causation is valid and demonstrates an interest in the problem. We believe that the idiopathic adult hypertrophy of the pylorus is a subclinical variety of true

congenital hypertrophy and that the concomitant form of hypertrophy may also be.

Uniformity in treatment of infantile hypertrophy of the pylorus is established. Cases of adult hypertrophy appear so infrequently that it is entirely possible for the surgeon to be faced with the problem for the first time without prior knowledge of its existence. In such a circumstance he has resorted to a variety of procedures in the past. In 1904, Maylord elected to do a gastroenterostomy to by-pass the stenosed pylorus. A pyloric slit 1½ inches long was made through the submucosa by Oliver in 1922. Bastianelli suggested the application of the Ramstedt sphincterotomy in 1925. A posterior gastroenterostomy was used by Crohn in 1928. Morton reported the cases of 2 patients treated by pyloroplasty and 1 treated by digital dilatation in 1930. One year later McClure reported the case of 1 patient treated by partial resection of the pylorus with plastic repair, 1 partial gastrectomy and 1 subtotal gastrectomy. Stone and Ruggles used the Fredet-Ramstedt technique on 2 patients in 1932. McNamee reported 2 cases in 1933, 1 patient treated by subtotal gastrectomy and 1 by Fredet-Ramstedt technique. Twenty cases reported by Judd and Thompson in 1933 were treated as follows: 10 pyloroplasties, 4 Fredet-Ramstedt, 6 pylorectomies, 1 parasympathectomy. In 1944, Wakefield reported resection of the pylorus in 1 case. In 1946, Vorhaus did a partial gastrectomy; in 1948 Mazzetti did a Hoffmeister-Finsterer gastric resection, and Katz reported the cases of 2 pátients both of whom received subtotal gastrectomy. In our cases the following operations were used: 1930, pyloroplasty; 1936, subtotal gastrectomy; 1948, Billroth I reconstruction following pylorectomy.

In 1948, Clagett and Waugh summarized their experiences with the Billroth I operation. They found that as familiarity with the operation increased they extended their indications for its application. They felt that one of the prerequisites for its employment is a mobile relatively normal duodenum. They believe that the Billroth I procedure has 4 advantages over gastrojejunal anastomosis after resection: (1) the operation is quicker and simpler; (2) there is no duodenal stump to turn in; (3) the duodenum has greater resistance to ulcer formation than the jejunum; (4) the physiology of the gastrointestinal tract is less disturbed. The safety of the Billroth I procedure was confirmed in a study made by Walters, Gray and Priestley; their statistics cover a period from 1907 to 1938 and compare all types of resections done for carcinoma of the stomach. Hospital mortality with Billroth I was 11.2 per cent; posterior Polya, 15.2 per cent; Billroth II, 17.6 per cent; anterior Polya, 17.8 per cent. Our election to do the Billroth I operation in the most recent case was due to the desire first, to remove the obstruction and second, to restore the normal continuity of the gastrointestinal tract in the absence of other disease. Wallager, Comfort, Weir and Osterberg made studies on the nutritional and functional results after various types of gastric resections. Their reports would indicate that patients who have lost the benefit of the proximal duodenum in normal digestion suffer more disturbances in motility, digestion, and nutrition than those treated by the Billroth I technique.

The Fredet-Ramstedt procedure has withstood the test of time in the infant; it has been used by a few surgeons in the adult form with satisfactory results, but we would hesitate to use it or to recommend its use for the following reasons: (1) the defect in the adult stomach would be fairly large and invite formation of a diverticulum; (2) inadvertent mucosal lacerations may heal with a cicatrix and give only partial relief from the obstruction; (3) hypertrophy of the pylorus is seen so infrequently in the adult that it may be confused with tumors whose eradication would be desirable. Pyloroplasty and digital dilatation would have similar contraindications as a mode of therapy. In addition, relief afforded by either may be only temporary. Gastroenterostomy would appear to be a simple solution, but in 1 of our cases symptoms returned within a 6 year period. In a study of the functions of the stomach following gastroenterostomy for pyloric obstruction Neuwelt, Medoff and Patidjl found that no constant changes were produced either in the volume of gastric secretion, acidity or emptying time. They found, too, that with partial obstruction gastroenterostomy could not be relied upon to produce either

rapid emptying of the stomach or decrease in acidity. Subtotal gastrectomy with gastrojejunostomy has been successfully employed, but we believe from our experience with the Billroth I type of pylorectomy that gastrectomy may be unnecessarily radical and physiologically not the most desirable method for the reconstruction of the gastrointestinal tract.

SUMMARY

1. A brief review of the subject of hypertrophy of the pyloric muscle in the adult has been presented. Theories concerning etiology are reviewed. Some features of the anatomy of the normal pylorus and the pathology of hypertrophy of the pyloric muscle are elaborated. Therapy as it has been applied over the years is summarized.

2. Classification of the adult forms of hypertrophy of the pyloric muscle as (a) idiopathic and (b) concomitant is proposed.

3. Three patients treated at St. Vincent Hospital from 1930 to 1948 are reported. In 2 of these failure of conservative surgical measures (gastroenterostomy and pyloroplasty) is emphasized.

4. Although of uncertain etiology, hypertrophy of the pylorus deserves a place as a clinical entity and should be included in the differential diagnosis in all patients with pyloric obstruction.

5. Since the changes are localized to the pylorus, and the duodenum is usually free and mobile, the Billroth I pylorectomy is particularly applicable in the surgical treatment of this condition.

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CONGENITAL ARTERIOVENOUS FISTULAS IN THE MANDIBLE

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THE great majority of arteriovenous fistulas are produced by accidental blunt or penetrating trauma. They may also be caused by surgical operations (2) or by mycotic arteritis (3). A certain number are congenital, although of 447 cases collected by Callander only 3 were of congenital origin. Reid reported 5 new cases of congenital arteriovenous fistulas in 1925, and 3 years later Pemberton and Saint described 9 additional cases. Embryonic communications between the primordia of arteries and those of veins are well known (8), and persistence of such channels seems to be the basis for congenital arteriovenous fistulas. This probably accounts for the fact that congenital fistulas usually have multiple arteriovenous openings, whereas a single opening is the rule in traumatic fistulas. As Pemberton and Saint pointed out, the head and neck are the commonest sites for persistence of such abnormal communications.

An arteriovenous fistula if untreated may lead to a number of well recognized complications: rupture with exsanguinating hemorrhage, sudden enlargement with gangrene of the part supplied, cardiac enlargement with failure, increased length of a limb, disfigurement due to a pulsating cirsoid mass, or endarteritis with septicemia (1, 5, 7, 9, 10). The surgeon is therefore obligated, if it is technically feasible without too great risk, to repair an arteriovenous fistula before one of these complications occurs.

Congenital arteriovenous fistulas of bone, although uncommon, have been described (5, 6), but no such lesion in the mandible has been reported. Gerbode and Holman did describe a case of a 6 year old child who had a congenital fistula between one internal maxillary artery and the ipsilateral pterygoid venous plexus with a thrill which was persistent unless both common carotid arteries were compressed simultaneously. As in Case 2, the internal jugular vein was a vestigial structure. In this child the mandible on the affected side was larger than its fellow, but bone erosion was absent, and presumably the actual arteriovenous communications were extramandibular. Also, it seems not unlikely that the mandible contained abnormal communications in Case 7 reported by Pemberton and Saint. This patient had 2 recurrences of pulsating masses of the chin and submental region following local excision of dilated vessels preceded by ligation of both external carotid arteries. No x-ray of the mandible was reported. Because they exemplify the exceptional difficulty of treating arteriovenous fistulas in bone and the special problems encountered when the mandible is the site of the lesion, the following 2 cases are reported.

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CASE REPORTS

CASE 1. E. H. (Unit No. 301440), a 29 year old white woman, entered the surgical service of the Johns Hopkins Hospital on September 7, 1943, because of a progressive swelling of the left side of the face since 1939. Throughout her life there had been a purplish discoloration on the left side of her face, regarded as a "birthmark," but this was asymptomatic until 1938. Then, during pregnancy, a small protuberance appeared in her left ear and bled so profusely that radium treatment was required to stop the bleeding. A year later a swelling of the left side of the face appeared and progressed slowly and intermittently, constantly accompanied by a roaring in the ear. Menstrual irregularities and exertional dyspnea manifested themselves over the next 4 years.

The patient had a purplish discoloration on the left side of her face where there was a soft compressible swelling extending over the mandible and the parotid region. Several small nodular swellings in the skin overlay this mass (Fig. 1). A continuous thrill and machinery murmur were present in the preauricular region, and these could not be obliterated by pressure on the tumor. No pulsation, swelling, or discoloration was present inside the mouth or pharynx. The pulse rate ranged from 80 to 90.

Roentgenologic examination of the chest showed no cardiac enlargement; films of the left mandible showed expansion of the ramus and part of the body

Fig. 1. Patient in Case 1 before operation, showing large mass over the left side of the face.

Fig. 2. Same patient 5 years after operation showing healed incision and greater facial symmetry despite resection of the mandible. The small cutaneous nodules were subsequently excised.

of this bone by a cystic process. An extramandibular soft tissue mass containing calcium deposits was also seen.

On September 10, the patient, under pentothal anesthesia, was operated upon through a left submandibular incision. The carotid bifurcation was identified and a tape was passed about the left common carotid artery. The external carotid was occluded by a bulldog clamp. The external jugular vein was divided, and the external carotid artery was traced distally. The superficial temporal branch was disclosed and divided. Multiple large arteries and veins were found to issue from a finger-tip sized defect in the mandible, and exploration in this region caused bleeding so forceful that large pieces of bone wax were blown out as soon as inserted. It was thus seen that the arteriovenous communications were inside the mandible. It was found that obstruction of the left common carotid artery did not diminish the bleeding. This observation suggested that the inferior alveolar arch was a major component of the arterial supply to this fistula. It was therefore necessary to resect the mandible from a point high on the ramus to one well out on the body. This procedure allowed prompt control of the bleeding and, for the first time, obliterated the thrill. Some dilated vascular channels in the left cheek were excised, and the wound was closed.

The patient's wound healed satisfactorily and she was able to take liquid diet from the third postoperative day. A weakness of the left corner of the mouth was present on discharge, but there was no thrill or murmur anywhere over the face or neck. Five and a half years later the patient returned to the hospital for excision for cosmetic reasons under local anesthesia of a dilated channel at the corner of the mouth. She was chewing well with good occlusion and without a prosthesis, and there was still no thrill or murmur. Figure 2 shows how symmetry had been restored to the face.

Case 2. R. B. (Unit No. 504247), a 43 year old white man, entered the Johns Hopkins Hospital on June 16, 1949, because of a pulsating lump on the left side of the neck and face. He recalled that as a child he had a "strawberry mark" on the left side of his face, but that it gradually disappeared completely. When he was 10 years old he first became aware of swelling and pulsation of this area associated with a roaring in the ear. He had long noted that the noise was louder and that he experienced discomfort in the left side of the face and neck, if he lay on his left side. Following the extraction of some left lower molars when he was 18 years old a hematoma in the sublingual region required incisions for evacuation. The patient thought the symptoms and the size of the mass were fairly constant until 1947 when he began to notice gradual enlargement of the left side of the face and neck with pain in this region on leaning forward. He was also aware of a pulse rate in excess of 100 for 2 to 3 hours following exercise. In the few months prior to admission there had been moderate exertional dyspnea and minimal edema of the ankles.

The patient had a fusiform enlargement of the left side of the face and neck, extending from the preauricular region to the supraclavicular fossa. Pulsation of moderate intensity was seen in this entire region. There was no abnormality of the overlying skin. A prominent vein extended up from the ear to the parietal region. There was no swelling, pulsation, or discoloration in the mouth or pharynx and the optic fundi were normal. A continuous thrill and murmur were everywhere detectable in this region with maximal intensity just below the angle of the mandible. Deep pressure at this point or on the very large common carotid artery on the left obliterated the thrill and murmur and slowed the pulse from 92 to 72. Gentle pressure in the supraclavicular fossa caused immediate ballooning out of a huge external jugular vein up to the parotid region. When thus obstructed, the external jugular vein was about 3 centimeters in diameter and demonstrated visible pulsations.

Roentgenologic examination of the chest showed no cardiac enlargement; the left mandible showed a

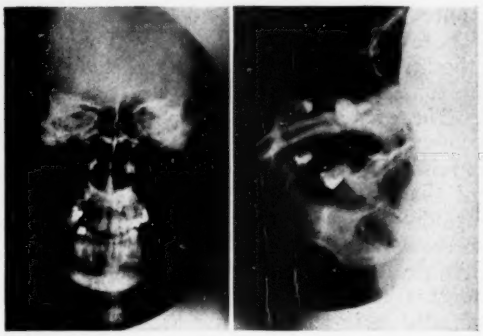

Fig. 3. Roentgenograms of patient in Case 2 showing erosion of the left mandible with a rim of calcification in the defect. This marks the site of the arteriovenous fistula.

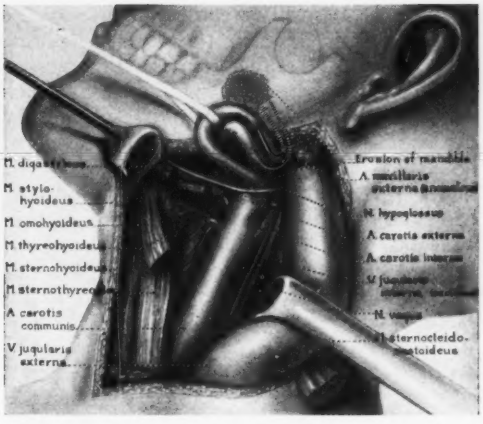

Fig. 4. Drawing of the operative field in patient in Case 2 just before resection of the anomalous artery and vein which may be seen entering the mandibular defect. The origin and initial course of the artery suggest an external maxillary. Note the vestigial internal jugular vein and the gigantic external jugular vein.

well defined area of bone erosion on the inner side of the ramus near the coronoid notch (Fig. 3). A rim of calcium was seen in close proximity to the area of bone destruction, presumably in the wall of an aneurysm.

On June 18, under nitrous oxide-oxygen-ether anesthesia the left side of the neck was explored through a vertical incision along the anterior border of the sternomastoid muscle extending from the clavicle to the preauricular region. The sternomastoid muscle was divided an inch above the clavicle and reflected to expose the carotid sheath. A tape was passed around the common carotid artery, which was 2 centimeters in diameter. Obstruction of this artery obliterated the thrill of the fistula. The external jugular vein, which was enormous, was left intact since the internal jugular vein, as in the case reported by Gerbode and Holman, was a vestigial cord. At the carotid bifurcation the internal carotid artery was of normal size while the external carotid continued upward as a structure almost as large as the common carotid. A tape was passed about the external carotid artery, occlusion of which obliterated the thrill of the fistula. The superior thyroid and lingual arteries were divided, and as the external carotid was traced upward, a large, tortuous artery was encountered protruding its elongated sigmoid segment down beneath the mandibular edge. It measured about 8 millimeters across, and in its upward concavity was located a slightly larger vein (Fig. 4). Since compression of this artery obliterated the thrill of the fistula, it was dissected back to its origin from the external carotid, with division of the stylohyoid muscle and posterior digastric belly, and preservation of the hypoglossal nerve. The point of origin of this large artery from the external carotid, together with the course of its first segment, suggested that it was the external maxillary artery. On tracing the artery and vein distally, however, it was found that they entered the roentgenographically demonstrated defect on the medial side of the mandibular ramus and that in the defect was a compressible sac, apparently containing the fistula itself. Since actually to remove the fistula would have necessitated resection of the mandible as in Case 1, and since the thrill and murmur could be obliterated by interrupting the large abnormal artery, the latter course was decided upon, and the tortuous artery was excised from its origin on the external carotid to its communication with the cirsoid mass in the mandibular defect. A segment of the unidentified vein accompanying the artery was similarly removed, and the wound was closed.

The wound healed satisfactorily and the thrill and murmur, both subjectively and objectively, were absent after operation. There was paralysis of the musculature supplied by the mandibular branch of the left facial nerve. The patient left the hospital asymptomatic on June 25, a week after operation. Three months later the preoperative asymmetry of the face and neck had almost completely disappeared, and the function of the mandibular branch of the facial nerve had fully returned. At this time there was a slight thrill and a soft continuous murmur over the fistula. These persisted after occlusion of the external jugular vein. Contrary to the preoperative finding, compression of the left common carotid artery produced no alteration in pulse rate, and the patient reported that his pulse rate at rest had fallen from a preoperative level of 92 to 95 to a postoperative rate of 70 to 75.

DISCUSSION

In those patients in whom arteriovenous communications exist in bone, once these channels are opened by dissection, removal of

the entire involved osseous segment may be the only way to control the profuse bleeding which comes forcefully from the large vessels which penetrate or lie in the bone. Such hemorrhage could be controlled temporarily in the case of an extremity by application of an arterial tourniquet about the limb at a higher level, provided only that the incompressible bone at this level does not contain abnormal vascular channels. Often, however, this set of favorable circumstances does not prevail, and certainly the method is not applicable to the mandible. This point is demonstrated by a patient operated upon by Dr. William P. Longmire, Jr. This patient had a congenital angiomatous change and multiple arteriovenous communications in the ulna of the right arm. Resection of the ulna was necessary to control profuse bleeding, which persisted even with occlusion of the subclavian artery and compression of the soft tissues about the humerus. Abnormal channels were present in the humerus as well. Furthermore, even if temporary control of such bleeding from the bone can be established, permanent control depends upon resection of the involved bone. Since the actual arteriovenous communications were within the defect in the mandible in the second patient reported here, resection of the involved portion of this bone would thus have been necessary to eradicate them. The condition encountered seemed ideal for treatment by removal of the major arterial blood supply since this could be accomplished by resection of a single large artery. It is our hope that no greater flow through the fistulas will recur than was evident after 3 months had elapsed. If a progressive increase in flow through collateral channels does occur, mandibular resection will be necessary to effect a complete cure. Mandibular resection is, however, a procedure not to be lightly undertaken, since it is deforming and extensive prosthetic work may be required to secure good postoperative function. The excellent result obtained without prosthesis in the first patient here reported is very fortunate and not the usual rule.

The existence of arteriovenous fistulas of the mandible in these 2 patients suggests the advisability of roentgenographic investigation of the mandible in any case of congenital arteriovenous communication in the face or neck, whether pressure does or does not obliterate the thrill. Should evidence of bone erosion be detected, preparation for mandibular resection must be made, since this may be the only way to control bleeding and to eradicate the fistulas. Such preparation should probably include dental impressions to be used if necessary in later preparation of a prosthetic device.

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THE MANAGEMENT OF MULTIPLE POLYPOSIS OF THE COLON

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THE importance of multiple polyposis (adenomatosis) of the colon cannot be overemphasized since it is almost invariably a fatal disease if unrecognized and untreated or if inadequately treated. It is the opinion of Mayo and Wakefield that the first clear description of true polyposis was given by Luschka in 1861.

Polyposis must be differentiated from multiple polyps arising in chronic inflammatory disease of the colon. This differentiation may at times be difficult since similar clinical pictures may be produced in both conditions and identical end results may ensue. Likewise, it must be differentiated from the very common form of polyps occurring singly or in small numbers. Polyposis is essentially a diffuse disease in which the lesions may be scattered in great numbers throughout the entire large bowel or there may be segments such as the rectum which may have either few or not any visible polyps at the time of initial examination. As will be mentioned subsequently, this does not mean that polyps will not become manifest at a later date in apparently uninvolved segments.

We are indebted to Lockhart-Mummery for the knowledge that this is a familial disease, not related to similar conditions produced by infection or ulceration, and handed down from one generation to another either as mendelian dominants or recessives.

The adenomas do not appear to form until puberty or after and ordinarily become manifest in the second, third, and fourth decades. Lockhart-Mummery also points out and it is likewise re-emphasized by others (4, 7) that the vast majority develop malignant degeneration of one or more of the adenomas unless prophylactic measures are employed to prevent this occurrence.

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With this fact in mind the importance of making a correct diagnosis and the prompt institution of adequate therapy is abundantly clear. One must suspect the possibility of the existence of the disease whenever the symptoms of mucus, diarrhea, and blood in the stools are present, ordinarily accompanied by loss of weight and strength. Examination then through the sigmoidoscope will reveal, if present, multiple polyps in the rectum, rectosigmoid, or both following which x-ray studies with barium and air contrast enemas may give evidence of widespread involvement of the rest of the colon. It goes without saying that biopsy should be made of any polyps within reach of the sigmoidoscope and suspicious of malignant degeneration since these findings will influence the order of the steps taken toward subsequent control of the disease.

If we are to avoid the almost certain development of carcinoma in these cases or hope to cure those in which malignancy is already present, some type of extensive large bowel resection will inevitably be necessary. There are several possible approaches to the problem, each having its advocates. Guptill and many others favor fulguration of polyps in the rectum and rectosigmoid when possible in combination with total colectomy and ileorectal or ileosigmoid anastomosis, with subsequent close observation of the retained segment.

The second principal approach to the problem involves resection of the rectum and colon accompanied by the formation of a permanent ileostomy and this view has many supporters with good reason. Ravitch and Sabiston (9) report a case of a patient dying of carcinoma of the rectum 8 years after colectomy, ileosigmoidostomy, and repeated fulgurations through the proctoscope and at the same time make the apt comment, "The disease is preponderantly familial, and a genetic predisposition to polyp formation should be expected

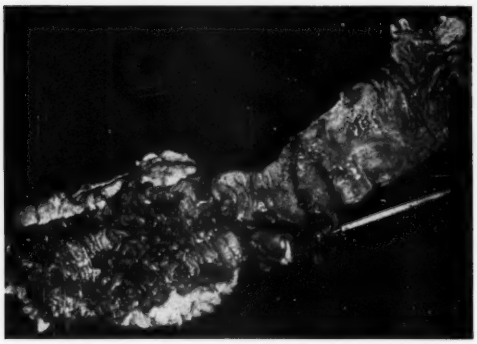

Fig. 1. Case 3. Abdominoperineal resection as first stage of total removal of large bowel for multiple polyposis. Pointer indicates undiagnosed carcinoma of rectosigmoid 2 centimeters in diameter.

to persist in this mucosa, however often it is fulgurated, with malignant degeneration constantly threatening as long as the patient lives.

"In short, multiple polypoid adenomatosis of the colon is a symptomatically troublesome condition with dangerous malignant potentialities. The only safe treatment is permanent eradication of the abnormal epithelium. When the entire colon is involved this means total colectomy." These authors are exploring the possibilities of anal ileostomy but as yet it would appear that the method requires further evaluation. Again, Ravitch (8) raises the very important question concerning the wisdom of doing a very extensive resection only to leave behind the very segment in which cancer most often develops.

Hoxworth and Slaughter, in their excellent article summarizing the 35 cases of radical resection for polyposis reported in the American literature since 1930, report that, in 4 of the 17 patients treated with preservation of rectum in addition to fulguration below, death resulted from cancer of the rectum in 1 to 6 years. This would certainly seem another strong argument for including the rectum almost without exception in the resection.

The analysis of these authors is in accord with our view that excellent results can be expected if an abdominoperineal resection is done as a first stage, followed in several weeks by colectomy and ileostomy at the second stage. The sequence of the resections would be varied, of course, if there were evidence that a carcinoma was already present in a segment other than rectum or sigmoid. In a few instances the entire large bowel has been resected successfully in one stage and while it is desirable to make the period of disability as short as possible, it will probably be found much safer in the great majority of cases to carry out the resection in at least two stages.

The disagreeable features of the standard permanent ileostomy have long been a deterrent to resection of the rectum when it could possibly be avoided, but now with the availability of the split thickness skin grafted ileostomy, as described by Dragstedt and employed subsequently by Sanders, ourselves, and others with great satisfaction, one should have little hesitation in resecting the rectum if this does in fact increase greatly patient's prospects of remaining permanently well.

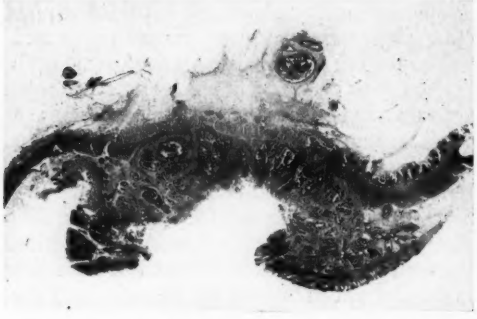

Fig. 2. Case 3. Low power photomicrograph of rectosigmoid carcinoma. Note cancer cells in lymphatic channel.

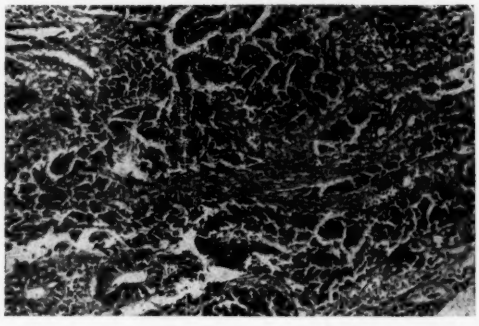

Fig. 3. Case 3. High power photomicrograph of rectosigmoid carcinoma.

Ileostomy openings flush with the skin surface and discharging directly onto it create a terrific problem of management and result in constant skin irritation, mental distress to the patient, and require much time and dressing for their care. The ileostomy of Cattell, the end result of which is a 1 inch stump of bowel protruding above the skin surface, is a step forward but nothing in our experience approaches the Dragstedt type of ileostomy.

Its advantages are direct drainage of ileal contents into a Koenig-Rutzen bag thus avoiding mess and irritation. The dilated distal ileum seems to act as a reservoir like the rectal ampulla with the result that the discharge is not continuous. It would seem that the opening through the abdominal wall produces some valve-like action, and it is noteworthy that our patients have not experienced cramps after about 3 weeks following operation.

Guptill has brought to 58 the number of reported cases of multiple polyposis treated surgically by modern methods and to this we add 3 cases with a brief summary of each.

CASE 1. T. A., aged 38 years, male, was admitted to Jefferson Barracks Veterans Hospital in January, 1948. In 1945 he first experienced rectal bleeding associated with a painful mass which protruded from rectum on defecation. Hemorrhoidectomy was performed in a station hospital but bleeding continued. The patient was re-examined and a diagnosis of multiple polyposis was made following which he was discharged from the army. He entered Hines Veterans Hospital later in 1945 and total colectomy was advised. For some reason this was not carried out and the symptoms improved.

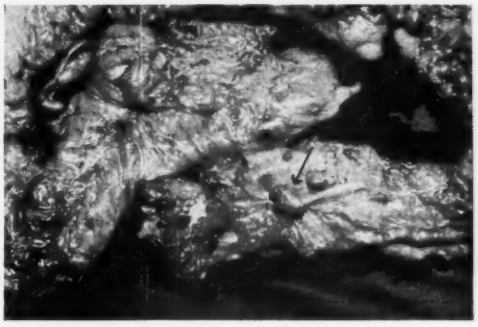

Fig. 4. Case 3. Remaining colon resected as second stage of total removal of large bowel. Arrow points to polyp in descending colon which has undergone malignant degeneration.

Rectal bleeding recurred 8 months previous to his admission at Jefferson Barracks in January, 1948. This was associated with 4 to 6 soft stools per day plus colicky pains in upper abdomen. Weight loss was 27 pounds. Family history indicated mother died of "cancer," site unknown. A diagnosis of multiple polyposis was substantiated and positive biopsy of rectosigmoid carcinoma was obtained.

Exploratory laparotomy was performed on February 11, 1948. Obvious large malignant masses were found in transverse colon and rectosigmoid with liver and mesenteric node metastases. Palliative resection of mass in transverse colon was performed because of impending obstruction. Transverse colostomy was made; uneventful postoperative recovery. Died from metastases in July, 1948.

Patient probably lost his life because resection was not carried out at the time multiple polyposis was first diagnosed 3 years before eventual death from 2 carcinomas.

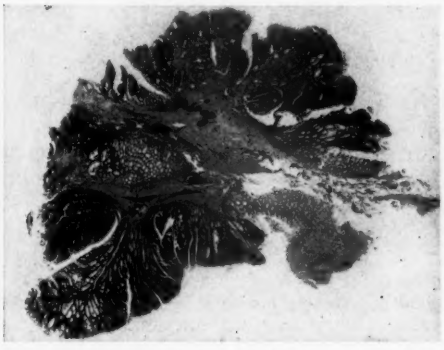

Fig. 5. Case 3. Low power photomicrograph of carcinoma in situ of descending colon.

Fig. 6. Case 3. High power photomicrograph of carcinoma in situ of descending colon.

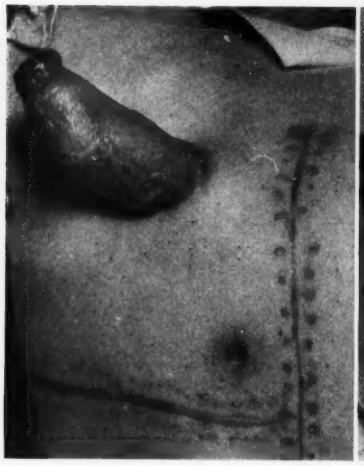

Fig. 7, left. Case 3. Anteroposterior view of split thickness skin grafted ileostomy of Dragstedt type.
Fig. 8. Case 3. Lateral view of split thickness skin grafted ileostomy.

Fig. 9, left. Case 3. Anteroposterior view of barium injected into ileostomy 6 weeks postoperatively showing ampulla-like dilatation of distal ileum.
Fig. 10. Case 3. Lateral view of barium injected into ileostomy.

CASE 2. J. B., aged 32 years, male, was admitted to Jefferson Barracks Veterans Hospital in May, 1948 with history from ages of 11 to 16 of much diarrhea frequently accompanied by mucus and blood. Symptoms recurred in 1945 in the Philippines. The patient was treated for "mucous colitis" with sulfasuxidine without improvement. In March, 1946 an obstructive lesion in the hepatic flexure was found at O'Reilly General Hospital and the right colon was resected with performance of ileotransversecolos-

tomy. No metastases were found. In March, 1947 an abdominoperineal resection was done at the Army and Navy General Hospital and the terminal descending colon was utilized for the colostomy. Pathological examination of the resected specimen showed multiple polyposis with malignant degeneration. In April, 1948 a routine examination of the colostomy using a sigmoidoscope produced a positive biopsy of a carcinoma in the descending colon. This one remaining segment of large bowel was resected at Jefferson Barracks Veterans Hospital and a skin grafted ileostomy of the Dragstedt type performed. Abdomen was still negative for metastases. Patient discharged in 3 weeks, well functioning ileostomy.

The true nature of the disease was not recognized until after the second major resection and with only the descending colon still remaining, a third carcinoma developed. The descending colon should have been resected earlier as an elective procedure.

CASE 3. F. B., aged 22 years, male, was admitted to Jefferson Barracks Veterans Hospital in June, 1948 complaining of frequent, grossly bloody diarrheal stools for the past 3 weeks. There had been occasional bleeding over the past year which the patient attributed to "piles." Family history was negative. Examination with the sigmoidoscope, barium and air contrast enemas established the diagnosis of multiple polyposis of the colon.

On June 18, 1948 we did an abdominoperineal resection and found a definite carcinoma the size of a 25 cent piece in the rectosigmoid. There were no metastases demonstrated. After an uneventful recovery we resected the rest of the colon August 13, 1948 and constructed a skin grafted ileostomy of the Dragstedt type. Pathologic study revealed multiple polyps in large numbers extending as far as the proximal transverse colon. In the descending colon we were able to identify grossly and microscopically another polyp which had undergone malignant degeneration. No metastases demonstrated. After a month the patient was discharged with a well functioning ileostomy and Koenig-Rutzen bag.

Surgical treatment was instituted as soon as the diagnosis was made in this case. This proved fortunate for the patient as 2 small undiagnosed carcinomas were encountered and removed in their early stages.

SUMMARY

Multiple polyposis of the colon is a familial disease. It is almost invariably fatal if unrecognized, untreated, or inadequately treated, since the development of carcinoma is practically certain without the institution of prophylactic measures.

The disease ordinarily manifests itself in the second, third, or fourth decades and should always be considered in the differential diagnosis of any condition producing diarrhea, mucus, and blood in the stools. Sigmoidoscopic examination in combination with barium and air contrast enemas will usually establish the diagnosis.

It is the consensus that treatment must consist either of colectomy and ileosigmoidostomy (or ileoproctostomy) in combination with fulguration of polyps in the lower segment followed by periodic observation, or resection of the rectum and colon in combination with permanent ileostomy.

We favor the latter plan since fatal carcinomas have been observed repeatedly to appear at a remote date in the retained rectal or rectosigmoid segment. As a secondary though still important consideration, the skin grafted ileostomy largely eliminates the horrors of the older type ileostomies and thus makes one less reluctant to sacrifice the rectum.

Three cases of multiple polyposis in different stages and treated surgically are added to the literature.

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OSTEOTOMY FOR CORRECTION OF DEFORMITY IN MARIE-STRUEMPELL ARTHRITIS

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OSTEOTOMY for correction of spinal deformity in Marie-Struempell arthritis yields outstanding results in selected cases. Restoration of nearly normal alignment is accomplished by direct operative attack upon the lumbar spine. This is the area of greatest deformity and the only area amenable to operative correction with any margin of safety. The anatomy of this region minimizes the neurological hazards.

Marie-Struempell spondylitis characteristically produces flexion deformity of the spine. More exactly, there is loss or reversal of the normal lumbar lordosis, increased dorsal round back, and a hyperextension deformity of the cervical region. Persistent care directed toward control of the lumbar element of the deformity may prevent the unsightly cosmetic effect of the disease. Exercises, periods of rest in the recumbent position, braces, and plaster jackets are some of the methods used to maintain or obtain improved spinal alignment.

Because of the protracted clinical course of the disease and its associated postural problem during a great part of the time, the patient is apt to pass into a state of deformity, especially if he is discouraged and relaxes his treatment and care. Despite modern medical knowledge, a patient with marked flexion deformity of the spine is seen from time to time. While bed rest and exercises may at times correct the situation, a certain number of these deformities do not respond to conservative treatment because of rigid fixation of the spine by actual bony ankylosis of the posterior elements. Besides an unsightly forward bent trunk, there is by necessity a compensating flexion deformity of the hips and knees and an attempt to hold the forward-pitched head high enough to see ahead. Often it is found that hip motion is actually limited in flexion and not infrequently the hip deformity requires surgical correction. If the hip flexion deformity requires surgical correction, it must be followed very shortly by spinal correction by any means in order to prevent its recurrence. There is rarely any fixed flexion deformity of the knees. Unless the actual involvement of the hips with the disease is severe, good hip posture is maintained after correction of the spinal deformity.

The possibility of overcorrection by any method must be kept in mind. If the thoracic spine presents marked flexion, there is compensating hyperextension of the cervical spine; in such alignment, overcorrection in the lumbar region makes it difficult for the patient to see his plate on the table or to read without holding the book at a high level. After the spine is rigidly ankylosed, constant struggle against flexion deformity is no longer a factor in the care of the patient, provided the spine has become fixed in good posture.

The patient with typical flexion deformity has much aching and soreness in joints that are not in good alignment. These joints are unable to tolerate the extraordinary stresses with the ease and lack of strain provided by normal postural alignment. Of course, spinal joints that have become solidly ankylosed are not painful, but often there are large areas that are still mobile and painful. This is especially true of the neck which usually ankyloses later in the disease. Vital capacity is diminished; the patient easily becomes dyspneic. Abdominal organs are pushed downward, all of which plus the debilitating tendency of the disease itself, adds to the exhausted state. Rarely do deformed patients have a feeling of well-being.

All patients should have the benefit of a trial of correction by conservative means under supervision as bed patients in a hospital.

From the Department of Orthopaedic Surgery of the Columbia University College of Physicians and Surgeons, the New York Orthopaedic Hospital, and the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital.

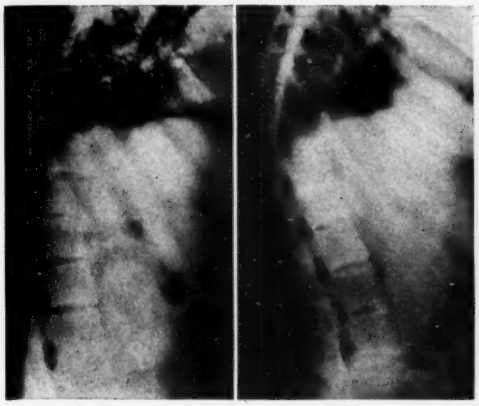

Fig. 1. Fig. 2.

Figs. 1 and 2. Case 2. Preoperative and postoperative roentgenograms showing posterior element of spontaneous fusion, deformity of spine, and the correction obtained at operation with large fusion mass posteriorly. Figure 1, left. Before operation. Figure 2. Seven years after operation.

The appearance of the spine by x-ray is not indicative of the amount of correction which may be obtained by conservative measures. There may be solid fusion of the posterior elements and yet little in the way of syndesmophytes on the bodies of the vertebrae; others may show extensive changes of both regions.

Osteotomy of the spine for the correction of deformity due to Marie-Struempell arthritis is not a common procedure. In early 1942, the authors observed the work being done on the problem by Dr. Smith-Petersen. Prior to this, the patient whose spine was solidly ankylosed in a position of flexion had no choice but to accept his unsightly deformity and the accompanying mental and physical aggravations. The value of osteotomy for a few of the many patients with this disease then under the care of the arthritis clinic of the New York Orthopaedic and the Presbyterian Hospitals was apparent.

From 1942 through 1945 five patients were selected for operation. All had had conservative treatment including hospital bed rest before the operation was considered. One operation was done in 1942, two in 1943, and two in 1945. The longest follow-up is 7 years, and the shortest 4 years. There were 3 males and 2 females with ages ranging from 27 to 38

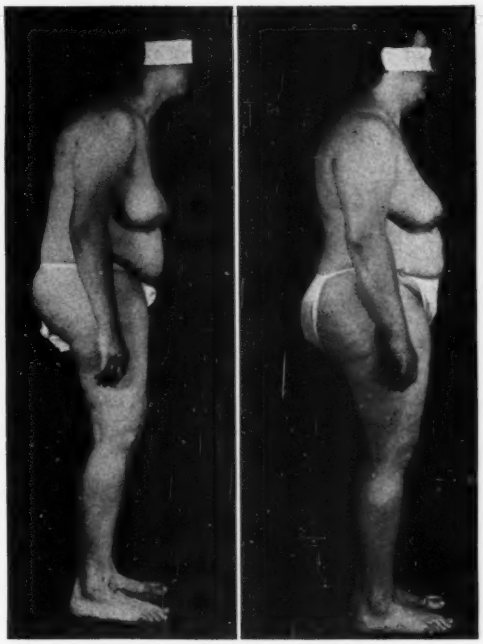

Fig. 3. Fig. 4.

Figs. 3 and 4. Case 2. Photographs adequately demonstrate excellent cosmetic result after 7 years of nearly normal activity after surgery. Figure 3, left. Before operation. Figure 4. Seven years after operation.

years. In so far as the spine was concerned, their deformities were severe. Examination of the peripheral joints indicated probable long periods of useful activity. Their arthritis was of long duration and apparently was not rapidly progressive. All patients had aggravation of symptoms in the neck and hips from stresses due to postural disalignment.

The activity of the arthritic process as indicated by the erythrocyte sedimentation rate (Westergren) varied considerably in these cases. In 3 instances, the sedimentation rate was below 30 millimeters per hour and in 1 it was below 20 millimeters per hour prior to operation. The sedimentation rate seemed to have no effect upon the result or the immediate reaction to surgery: conversely, surgery seemed to have no effect upon the pattern of the erythrocyte sedimentation rate.

All osteotomies were done through the lumbar spine with osteotomy sites at the level of

the first and second lumbar vertebrae in 2 instances, second and third lumbar in 3, third and fourth lumbar in 2 and fourth and fifth lumbar in 1. In 3 cases double osteotomy was performed; in 2 cases, single osteotomy was performed.

OPERATION

Orientation for the site of osteotomy was accomplished by marker roentgenograms. The fracture table upon which the operation was performed was under control of a surgeon who understood its mechanics thoroughly and also the objective of the operating surgeon. By subperiosteal dissection, the posterior column of the bone was exposed over its entire width at the site selected. The spinous processes were removed and utilized later for chip grafts to reinforce the osteotomy site. A transverse wedge of bone was removed, this wedge extending across from the mid-dorsal point of each foramen further to insure against any possibility of nerve root compression. The gap thus created, measuring about 3/8 inch in width, was allowed to close slowly under direct vision and control of the operator.

An accurate estimate of the alignment of the spinal column could now be made and if necessary either the gap enlarged if feasible, or another osteotomy made to obtain the lumbar lordosis necessary for the re-establishment of good posture. Following closure of the incision, the corrected position was maintained by a plaster jacket extending from the manubrium to the knees. Eight weeks after the operation, patients were ambulant in a plaster body jacket which was continued until the osteotomy sites were seen to be solidly united in the roentgenograms; this required on the average 6 months.

DISCUSSION

Patients selected for this operation were felt to have a worthwhile span of future usefulness to justify the procedure. Their deformity had failed to respond to adequate conservative attempts at correction. The arthritis was not rapidly progressing and all had relatively good function in joints of their extremities. All 5 patients tolerated the procedure very well and were gratified with the improvement in general appearance. The relief of the symptoms of strain on the motor skeletal system from the resumption of a more normal posture has been one of the outstanding results of the operation. No patient has had recurrence of flexion deformity. At the present time, all are engaged in useful full time occupations, namely: (1) postoffice clerk, (2) clerical work—patient also dances and rides horseback, (3) housewife, (4) airplane mechanic, (5) short-order cook.

CASE REPORTS

CASE 1. G. F., a 36 year old woman, was first admitted to the New York Orthopaedic Hospital on April 9, 1942 with a severe flexion deformity of the dorsolumbar spine and complaining especially of pain and fatigue in the cervical region. Symptoms of arthritis had begun at age 16, and her flexion deformity had been present since the age of 20. On June 19, 1942, an open right hip flexion release was done for a hip flexion deformity which had not responded to conservative treatment. The flexion of the spine had not responded to rest designed to gain extension. Roentgenograms showed a fusion of the posterior elements of the dorsolumbar spine without very extensive calcification of the anterior longitudinal ligament. The arthritis seemed to be confined to the spine, sacroiliacs, and to a lesser degree to the hips. This seemed an ideal situation for correction of the spinal deformity by open operation, so on September 28, 1942, an osteotomy was done at the level of the first and second lumbar and second and third lumbar interspaces. Correction was easily obtained. On December 4, 1942, the patient became ambulant in a body cast. All immobilization including braces was discontinued at 6 months. Operative findings: posterior elements had been converted into one continuously solid column of bone. Agglutination test was negative for streptococcus. Sedimentation rates were normal during period of our observation.

Six years after operation, the correction gained at operation had been maintained. Her hips which at the time of the spinal procedure extended to 165 degrees now extended to 180 degrees. Her neck is symptom free, and while motion is limited, she can look down at her feet and face upward at about 15 degrees above the horizontal. She works as a secretary, swims, dances, and rides horseback for recreation.

CASE 2. G. D., a 35 year old housewife, had onset of backache at age of 15. At 25 years of age, she had developed a flexion deformity of the spine that required her to stand with her hips and knees flexed to maintain standing balance. When first seen at the New York Orthopaedic Hospital in early 1943, she had a fixed flexion deformity of the dorsolumbar spine. The hips had good motion except for slight flexion deformity. The cervical spine had only moderate limitation, but ached and fatigued easily when she was up and about. She was ad-

Fig. 5.

Fig. 6.

Figs. 5 and 6. Case 3. Preoperative and postoperative roentgenograms showing deformity, posterior element fusion, and calcification of anterior longitudinal ligament and correction obtained. Figure 5, left. Before operation. Figure 6. Six years after operation.

mitted and treated by bed rest for 2 months in an attempt to gain conservative correction of the deformity, but no spinal change could be brought about. On April 2, 1943, an osteotomy was done at the third and fourth lumbar interspace. Immobilization was discontinued 5 months after operation. This patient has an older brother under care of this clinic with a severe, advanced Marie-Struempell arthritis. The patient's sedimentation rate has varied between 20 and 50 while under observation in this clinic. Agglutination test was negative for streptococcus. In spite of apparent activity of the disease at the time of operation as evidenced by a sedimentation rate of 40, the course of the disease was not adversely affected by the operation. Operative findings revealed that the posterior elements had been converted into a continuously solid column of bone.

Six years after operation, the patient does her own housework without difficulty. She is the mother of 2 children born prior to the operation. She walks erect. Hip motion is satisfactory with good flexion and extension. Peripheral joints remain free of disease. The correction at operation has been maintained.

CASE 3. L. R., a 43 year old male clerk, had onset of arthritis at the age of 23. For 11 years prior to admission to this hospital in April, 1943, the patient had had a severe forward flexion deformity of the spine (dorsolumbar). His neck was especially painful when he was up and about and it was with effort that he could look ahead. The hips extended to 165 degrees, but had rather good motion. All peripheral joints were free of disease. Roentgenograms showed fusion of the posterior elements and calcification of the anterior longitudinal ligament in the dorsal and lumbar spine. On April 12, 1943,

Fig. 7. Fig. 8.

Figs. 7 and 8. Case 3. Photographs demonstrating excellent cosmetic result and establishment of apparently normal posture which has been maintained for 6 years following surgery. Figure 7, left. Before operation. Figure 8. Six years after operation.

osteotomies were done at the level of the first and second lumbar interspace and second and third lumbar interspace. As the patient was hyperextended, snapping sounds were heard, presumably the separating of the calcified anterior longitudinal ligament. All immobilization was discontinued at 6 months. Agglutination test was negative for streptococcus. The sedimentation rates have varied from 15 to 30 since he has been under our observation.

Seven years after operation, the patient is free of discomfort in his cervical region. The corrected position has been maintained. He stands erect. His peripheral joints remain free of disease. He works as a clerk. His hips extend to 170 degrees, but the lumbar lordosis enables him to stand straight.

CASE 4. J. N., a 27 year old male mechanic, had onset of arthritis at age of 19 years. For 4 years prior to admission, he had had a marked flexion deformity

of the dorsolumbar spine. Except for mild hip joint involvement, all other joints were free of disease. Roentgenograms revealed marked decalcification of the anterior longitudinal ligament and a continuous solid fusion of the posterior elements. On October 12, 1945, a transverse osteotomy at the second and third lumbar interspace was done and correction obtained. All immobilization was discontinued at 6 months. Sedimentation rate has varied between 20 and 35.

Three and a half years after operation, this patient is working as an airplane mechanic without the neck and posterior thigh symptoms which were so bothersome preoperatively. The peripheral joints remain free of disease. The patient walks erect and the correction gained at operation has been maintained.

CASE 5. R. E., a 39 year old male mechanic, had onset of arthritis at age of 20 years. For 8 years prior to admission to this hospital, he had a flexion deformity of the dorsolumbar spine. X-ray findings were those of advanced Marie-Struempell arthritis of the dorsal lumbar spine. On November 23, 1945, an osteotomy was done at the level of the second and third and fourth and fifth lumbar interspaces. Immobilization was completely discarded at 6 months. During observation in this clinic, his sedimentation rate has not gone above 30.

Three years after operation, he is working regularly as a mechanic. He has no neck or posterior thigh discomfort. His posture is satisfactory and the correction obtained at operation is still maintained.

CONCLUSION

1. The results of operative correction of fixed flexion deformity of the spine in 5 patients with Marie-Struempell arthritis have been presented. The improvement has been symptomatic, cosmetic, and functional; the correction has been permanent.

2. Three have been followed more than 6 years, and 2 others for 4 years.

3. In the experience of this clinic, the operation presented has a definite place in the rehabilitation of certain patients with fixed flexion deformity of the spine due to Marie-Struempell arthritis.

SURGICAL EMERGENCIES IN GYNECOLOGY AND OBSTETRICS

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MANY mistakes have been made in the handling of acute surgical lesions which are encountered in a gynecological or obstetrical practice. These errors in management can be attributed to: (1) incomplete medical investigation before the active surgical treatment is instigated; (2) errors in judgment. These errors are usually due to the fact that the operator is a surgeon who lacks experience in the management of obstetrical or true gynecological conditions, or, not infrequently, is a gynecologist who has had insufficient experience in the handling of acute surgical lesions which lie somewhat outside the realm of ordinary gynecological practice.

For example, it is a not uncommon experience to be told about some patient who has been subjected to an incorrect operative approach because her doctor opened the abdomen suspecting a genital lesion, but was surprised to find a neoplasm of the bowel. In most instances this error could have been prevented by a complete preoperative investigation which should include, in a problem patient, a barium enema and sigmoidoscopic examination (1). You have also heard of the surgeon who has had a sketchy training in obstetrics and gynecology and who has removed one or both ovaries thinking there was some pathological lesion present when actually the condition was a physiological process, such as a recently ruptured graafian follicle or a corpus luteum which was somewhat larger than normal. Probably the most serious situation is a maternal mortality following cesarean operation in a case in which delivery per vaginam was preferable.

These facts emphasize the importance of adequate training for any surgeon who is permitted to open the abdomen. In addition, the general surgeon and gynecologist should be encouraged to become more familiar with conditions which are not frequently encountered in their daily routine.

It is interesting to observe just how frequently general surgical conditions occur in a gynecological practice. For example, the total number of admissions to our gynecological service of the Royal Victoria Montreal Maternity Hospital during 1947 and 1948 was 3,707. All patients were admitted with a tentative diagnosis of a gynecological condition. There were 56 cases in which this diagnosis was found to be either partially or totally incorrect. The admission diagnoses included: (1) pelvic inflammation, (2) fibroma of the uterus, (3) ovarian neoplasm, (4) endometriosis.

In some of these cases a single surgical lesion was found to be present while in others a gynecological condition was coincidental. However, in all instances the general surgical lesion was considered the more important. Following are the final diagnoses made in these 56 cases: appendicitis in 11 cases (acute with abscess in 4 patients and acute with unruptured appendix in 7 patients); diverticulitis in 17 patients (treated medically in 15, abscess treated by colpotomy in 2 patients); acute urinary infection or calculi in 14 patients; cholelithiasis in 1 patient; cancer of gastrointestinal tract in 9 patients; and carcinoma of the breast in 4 patients.

In this group of 56 cases our preoperative investigation aided in making an accurate diagnosis in 49 individuals. There were 7 instances in which we should be criticized for incomplete preoperative investigation or for the lack of good surgical judgment; the actual diagnosis was made at the time of or following operation. There were 2 cases in which the abdomen was opened with a tentative diagnosis of twisted ovarian cyst and tubal pregnancy; the final diagnosis was ruptured appendix in both instances. In 1 case a posterior

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colpotomy was performed for drainage of a pelvic abscess which was taken to be tubal in origin. It was found to be a ruptured diverticulum of the sigmoid and subsequently was complicated by a fecal fistula (9). Two other patients were finally found to have cancer of the sigmoid but they were operated upon with the preliminary diagnosis of ovarian neoplasm and endometriosis. Four patients were admitted with a diagnosis of fibromyomas of the uterus. In 2 instances nodules were discovered in the breast, operation for this condition was carried out promptly, and a diagnosis of carcinoma was made. The other 2 individuals had a hysterectomy for fibroids and, by fortunate chance, nodules in the breast which proved to be carcinoma were discovered during the postoperative stay of the patients in hospital. It would have been better if this condition had been diagnosed before the pelvic operation.

During the same 2 year period in a group of 7,147 obstetrical patients, extraordinary surgical conditions occurred in 26 cases. These acute surgical complications developed during pregnancy and operative therapy was given at that time. In only 3 cases of cholelithiasis was operation postponed to 1 month postpartum. These complications included: carcinoma of cervix in 1 case; ruptured uterus in 1 case; acute appendicitis in 6 cases; intestinal obstruction (adhesions) in 2 cases; urinary calculi in 5 cases; papilloma of bladder in 2 cases; gastrointestinal cancer in 3 cases; perforated gastric ulcer in 1 case; subarachnoid hemorrhage in 1 case; removal of ruptured intravertebral disc in 1 case; and cholelithiasis in 3 cases. These figures show conclusively that pregnancy does not give immunity to the occurrence of acute surgical emergencies (8).

Two conditions which are primarily gynecological and which frequently complicate pregnancy are uterine fibromyomas and ovarian cysts. Management of these conditions plays an important role in the eventual result (5). In a 5 year period from 1944 through 1948, our records show that fibromyomas of the uterus much more frequently than unilateral and bilateral ovarian cysts complicate pregnancy (6). In 15,949 obstetrical cases there were 211 fibromyomas complicating pregnancy and 24 unilateral or bilateral ovarian cysts.

The method of treatment for the obstetrical patient with fibroids varies considerably from that used when an ovarian cyst is the complicating factor. When fibroids are present, management should be of an expectant nature. Progress of a normal pregnancy and delivery should not be made abnormal by some meddlesome obstetrician. Only when the patient experiences repeated attacks of acute pain, vomiting, or fever should myomectomy be considered during the pregnancy. Adequate sedation and bed rest are invaluable for the relief of pain and the prevention of subsequent attacks. We believe that repeated doses of morphine are most efficacious. Papaverine has been recommended by Perel in France on the basis that it is more efficient as an antispasmodic drug. We do not use progesterone or estrogens as a prophylactic measure because there is no deficiency found in this type of case.

Delivery per vaginam may be carried out in the presence of fibroids provided there is no obstruction offered the fetus in the birth canal. Because of the possibility of degeneration, removal of larger fibroids should be considered and such removal can be accomplished toward the end of term by means of a cesarean operation (3, 4).

Our treatment of 211 obstetrical patients with fibroids was as follows: cesarean section with hysterectomy was performed in 29 cases; myomectomy with cesarean section in 24 cases; myomectomy during pregnancy in 16 cases; and delivery per vaginam in 156 cases.

If a myomectomy is indicated during the pregnancy, most authorities agree whenever it is possible that it should be performed after the 90th day of pregnancy. The uterus is less irritable and placental function is well established by this time. We follow the rule that a cesarean section should be the method of delivery following those cases of myomectomy in which the fibroids are intramural. When they are situated subserous or are pedunculated delivery per vaginam is recommended.

One may ask if it is necessary to do a cesarean at any time following myomectomy. Accidents do occur. One of our patients had a myomectomy for intramural fibroids in 1945. Three years later when the patient was 8 months pregnant she was seized with a sudden sharp pain which was followed by profound shock. A cesarean operation was performed 2 hours later at which time a rupture of the old scar 5 centimeters in length was found accompanied by massive intra-abdominal hemorrhage and the baby was delivered dead. Fortunately the mother survived.

Our results show that in a total of 211 cases no mothers were lost. There were 11 cases in which a living baby was not obtained—an incidence of 5 per cent. Five of them were included in the operative group—2 were abortions after myomectomy, 2 were nonviable, and 1 was the case in which the uterus ruptured at 8 months' gestation.

When there is an ovarian cyst of any appreciable size—6 centimeters in diameter or larger—and the patient has an intrauterine pregnancy, she should be treated somewhat differently. Complications are prone to occur due to twists in the pedicle with consequent impairment of circulation in the predelivery or postdelivery state. Obstruction to labor is not infrequent. Some authors suggest removal of all ovarian cysts at around 12 weeks of pregnancy. We agree that if there is a suggestion of any such complication, operation is indicated. Of the 24 cases which were diagnosed during the 5 year period 12 patients came to operation at some time during the pregnancy.

It is most essential to diagnose these cases in early pregnancy because they are difficult to detect in later months. Otherwise they may be inaccurately diagnosed as fibroids of the uterus. By pelvic examination in the first 3 months of pregnancy an accurate diagnosis can usually be made. X-ray examination is an aid in this type of case because approximately 50 per cent of cysts which occur in pregnancy are dermoid in origin and they usually contain radio-opaque material.

There were 4 individuals in whose case both ovaries were removed because of the presence of large bilateral dermoid cysts (2, 11). Two of these patients were operated upon before 90 days' gestation. Most certainly it is important that these patients be given sedation during the preoperative and postoperative period.

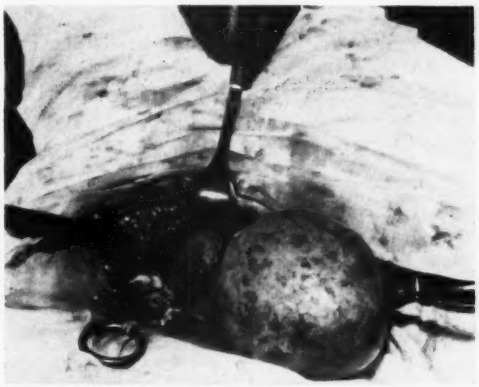

Fig. 1. Case 2. Large cyst of right ovary and smaller irregular cyst of left ovary (just above ring, left below).

In addition, if there is any indication that the corpus luteum has been removed along with the cyst these patients are benefited by large doses of progesterone and estrogenic substances. We prefer the intramuscular administration of progesterone in amounts not less than 50 milligrams per day. This may be used in conjunction with the oral administration of diethylstilbestrol (12).

Dangers of abortion after 90 days of pregnancy are not great. The placental function is well established and progesterone production is carried on by the placenta (7).

None of our patients with ovarian cysts had an abortion postoperatively. One patient who had a bilateral oophorectomy at 85 days' gestation was given 100 milligrams of progesterone each day for 4 months. She carried the child until term and she was allowed to go into labor. Unfortunately, after a very few mild contractions the fetus stopped moving and it was deadborn in spite of an apparently normal development. For this reason our second patient who had a bilateral oophorectomy at approximately 70 days' gestation was delivered at term by means of a cesarean. A healthy infant weighing 3,020 grams was born.

CASE REPORTS

CASE 1. In this patient the pregnanediol glucuronidase excretion after bilateral removal of the ovaries was noted as follows:

No. of days after menses	Pregnanediol glucuronidase excretion in 24 hours—milligrams
85	9.4
87 ..... operation	
92	5.5
93	8.0
96	10.2
112	7.6
117	14.6
120 ..... therapy ceased	
125	19.5
273 ..... normal delivery	

Patient had her last menses on October 2 and operation was performed on December 28. At the time of operation the uterus was the size of a 10 weeks' pregnancy. There were large bilateral cysts of the ovaries with twists of the pedicle on both sides. Both ovaries were removed. Medication consisted of repeated doses of morphine postoperatively and daily intramuscular injections of 25 milligrams of progesterone along with 10,000 units of estradiol benzoate for 21 days. A living and normal baby of 3,670 grams was delivered per vaginam at full term. An adherent placenta necessitated manual removal.

CASE 2. This patient (Fig. 1) had her last menses on February 9. Bilateral oophorectomy was performed on April 15 (75 days); cesarean section, on November 16 (270 days). She experienced recurring attacks of acute pain with vomiting. Laparotomy revealed a very large cyst of the right ovary with a smaller irregular cyst of the left ovary. Both ovaries were removed and the pathological diagnosis showed the cysts to be teratoid tumors. Medication included morphine postoperatively with daily intramuscular injections of 50 milligrams of progesterone for 21 days. This was followed by oral administration of 25 milligrams of stilbestrol each day for 3 months. A normal baby weighing 3,020 grams was delivered by cesarean section at term.

SUMMARY

1. Obstetrical patients are not immune to developing general surgical complications.

2. When fibroids occur in combination with pregnancy expectant treatment is advised.

3. Ovarian cysts may cause acute complications in pregnancy or immediately postpartum.

4. The general surgeon and the gynecologist should be encouraged to become more familiar with those conditions which are not frequently encountered in routine practice.

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IDENTIFICATION OF REGIONAL LYMPH NODES BY MEANS OF A VITAL STAINING DYE DURING SURGERY OF GASTRIC CANCER

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ALTHOUGH excision of the regional lymph nodes is generally recognized as one of the most important considerations in the surgical treatment of carcinoma, there are difficulties which beset the surgeon in some situations which make its accomplishment very difficult, or even impossible. For example, the nodes along the internal mammary artery are seldom if ever exposed during the operation of "radical" mastectomy in the treatment of cancer of the breast. The regional nodes of the stomach more nearly approach the ideal of accessibility than do the nodes of most of the other viscera commonly involved in carcinoma. Here is a situation in which the immediate regional or primary nodes are located within the abdomen or near the lower part of the esophagus, all within reach through the exposure required for excision of the stomach (Fig. 2). Yet many of the nodes which should logically be removed are seldom seen at operation. The reasons for this are several: the small size of the nodes, the similarity of their color and consistency to that of the areolar and adipose tissues in which they are enmeshed; and in many cases, the inadequacy of the exposure for the identification of some of the nodes such as those in the neighborhood of the celiac axis and the paraesophageal region. One of us (JW), in seeking a means of tagging the nodes to make them more easily recognized at surgery, recalled an article by Braithwaite, who described a method of mapping lymph nodes in vivo by injecting a dye into the cecal wall and noting its uptake by the nodes which receive lymph from the injected area. Braithwaite's purpose in making the study was to ascertain whether or not there was a causal relationship between appendicitis and duodenal ulcer through the medium of lymphatic connections. It occurred to us that this procedure offered an ideal means of identifying otherwise obscure nodes during operations for the extirpation of cancer.

Fig. 1. Stained lymph nodes from specimen shown in Figure 4. Small node, left, shows no gross evidence of malignancy. The entire node has taken the stain. The middle node shows gross malignancy at each pole and only the middle uninvolved portion of the node has received the stain. The large node on the right is almost completely replaced by cancer tissue and only the periphery of the node has taken the dye.

This means of identifying nodes should be particularly useful in the surgical treatment of carcinoma of the stomach for the reasons already mentioned. Most of our investigations have been concerned with this viscus since the beginning of the study; but we have more recently extended it to other regions, including the lung, the colon, the neck, and the inguinal region. Studies in still other regions have been initiated and will be reported in later communications. Our present remarks will be limited to the studies involving the stomach.

Braithwaite used indigo carmine in his investigations, and while it was a satisfactory means of attaining his objective, there were

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Fig. 2. Schema of primary nodes receiving lymph from the stomach. Large solid dots represent nodes seen from anterior view. Small dots circled by broken lines represent nodes posterior to stomach. This diagram is a composite of stained nodes seen in the various cases in a series of 34.

difficulties attending its use which made it short of ideal for our purpose. The dye is taken up slowly and adequate staining of the nodes is not always attained during the course of the operation. This could be due to unsuitable staining properties of indigo carmine, to unsatisfactory methods of injection, or to the failure of the nodes to retain the dye after they receive it. A satisfactory dye would be one which is quickly taken up by the nodes, which stains intensely, which is more or less specifically taken up and retained by the nodes and is nontoxic. While we were searching for a dye which would most likely fulfill these requirements, Dr. Travis Winsor directed our attention to pontamine sky blue, a dye which had been used by McMaster and Parsons in studies on the manner of lymph flow in mice. This dye gives a deep bright blue color in high dilutions. It does not change color within the limits of the acidity and the alkalinity of the body tissues and fluids, and it is nontoxic as determined by half-lethal tests in mice and other tests which we have made with it. A report on the pharmacological properties of the dye is now in preparation. Prior to using this dye we used a suspension of fine carbon particles because of the success one of us (JW) had with it in tracing abdominal lymphatic patterns in rabbits. However, we were disappointed to find that the particles were taken up too slowly to be suitable for use during surgery.

Most of our studies since then have been with pontamine sky blue. We have made occasional minor alterations in the technique as our studies progressed, and have tried other dyes, in an effort to improve the results. The procedure as it is now developed, however, is of such great aid in dealing with actual and potential lymphatic extensions of carcinoma that we have adopted it as a routine procedure in radical gastrectomy.

Injections have been made in 34 operations involving the stomach, up to the time of this report. Twelve of these were cases of carcinoma of the stomach, in which radical total gastrectomy was performed in 10 and subtotal resection was performed in 2. Six were nonresectable cancerous lesions. Sixteen were gastric ulcers in which local excision of the ulcer or subtotal resection was performed.

The procedure is carried out in the following manner. Four or 5 cubic centimeters of a 2 per cent solution of the dye is injected into the anterior wall of the stomach as soon as the abdomen is opened and the diagnosis is established. The injections are made near the greater and lesser curvatures of the stomach by means of a Luer syringe of the tuberculin type, fitted with a fine (26 gauge) needle (Fig. 3). The dye is instilled into the muscularis rather than into the subserosa, because the tone and contraction waves and the vascular pulsations in the muscular layer should tend to accelerate the flow of the dye-stained lymph to the regional nodes (2). The injection is made slowly to minimize puddling of the dye solution at the site of the injection. While the injection is being made, streaks of dye are often observed traversing small lymph

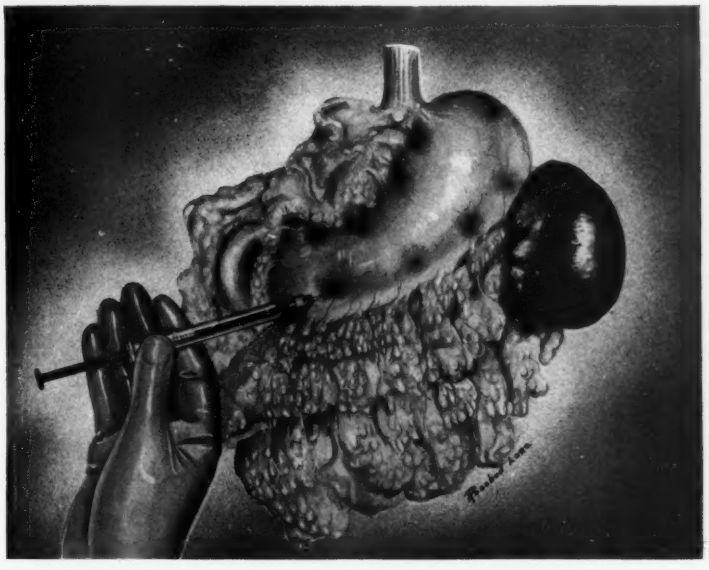

Fig. 3. Method of injection of the dye solution into the muscularis of the stomach. Several injections are made near the greater and lesser curvatures.

channels on the surface of the stomach and its omental and ligamentous attachments. If staining of one or more of the groups of regional nodes is not seen within the first few minutes, a second injection is made with the same dosage at sites adjacent to the original injections.

One then proceeds with the gastrectomy. It is now our practice to perform radical total gastrectomy in resectable gastric carcinoma, including a portion of the esophagus and duodenum, the spleen, the greater omentum and the lesser omentum (Fig. 4). Subtotal resection is performed only in those cases in which the cancerous involvement is so extensive that the resection can be no more than palliative, or in cases in which the general condition of the patient makes radical total extirpation too hazardous. The extirpation is not started until 10 to 15 minutes after the injection is completed in order to allow time for the passage of the dye from the stomach to the regional nodes. The severance of the major arteries and veins supplying the stomach is delayed for another few minutes since the major lymphatic vessels follow the blood vessels more or less closely, and too early division of the vessels and their associated lymphatics might interfere with the passage of the dye to the nodes. In the meantime,

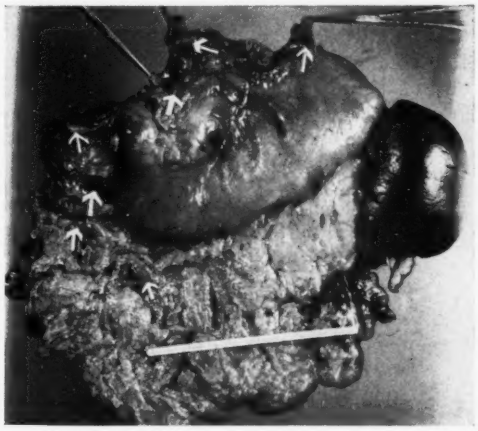

Fig. 4. Radical gastrectomy including spleen, greater omentum, most of lesser omentum and part of esophagus and duodenum. The bloc resection includes areolar tissue over the celiac axis and along the lower part of the esophagus. Stained nodes were seen in these areas at operation. Arrows point to some of the groups of stained nodes.

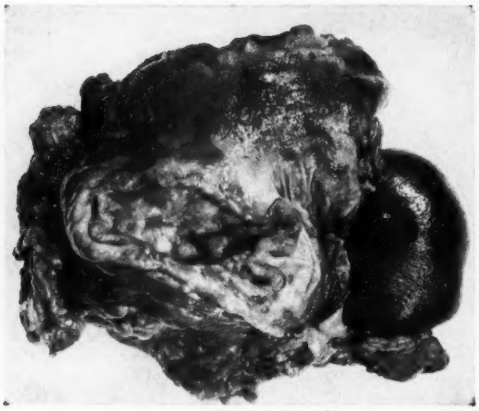

Fig. 5a.

Fig. 5b.

Fig. 5. a, Photograph of resected specimen of radical gastrectomy including part of duodenum and esophagus, spleen, tail of pancreas, midportion of transverse colon, greater omentum, and most of lesser omentum. The stomach and related structures are distorted by the large fungating carcinoma of the greater curvature. b, Diagram of nodes seen in Figure 5a. The large solid dots and the small dots circled with broken lines represent anterior and posterior stained nodes, respectively. The circled clear areas and the circled crosses represent anterior and posterior unstained nodes respectively. Most of the unstained nodes were not seen at operation.

excessive manipulation of the stomach is avoided in order to minimize the possibility of breaking off particles of cancer tissue into the circulation. While it might be objected that the delay in dividing major vessels may contribute to the dissemination of cancer during the operative procedure, it is our opinion that the benefit gained by the staining of the nodes more than offsets this hazard. As the dissection proceeds, groups of stained nodes come into view and these together with neighboring unstained nodes are included with the specimen which is being removed. Great care is exercised to avoid injury to the hepatic artery and the celiac axis in removing nodes along their course. The entire specimen is removed in a single mass if possible. After its removal a careful search is made for nodes which might have been overlooked, particularly along the portal vein, in the region of the common duct and pancreas, and along the remaining lower esophagus.

With our present method of injecting along both curvatures of the stomach we have been able to demonstrate stained nodes in the region of all of the major vessels supplying the stomach, including the right and left gastroepiploic arteries; gastric tributaries of portal vein; the gastroduodenal, right gastric, hepatic, and left gastric arteries; and the short branches of the lienal artery to the cardiofundic region of the stomach (Fig. 5, a and b). Nodes have also been identified in the splenic pedicle, along the lower part of the esophagus, over the surface of the pancreas, along the common duct, and along the portal vein. One or more of these groups at times has failed to take the stain. As our technique has improved, however, the failures have decreased.

If the injection is limited to one or two segments of the stomach, the staining of nodes is limited accordingly. Thus, if the injection is confined to the right half of the stomach, only those nodes receiving lymph directly from the right half of the stomach become stained (Fig. 6, a and b).

Injection of the dye into a particular area of the stomach usually results in the staining of the group of nodes which would be expected

Fig. 6a.

Fig. 6b.

Fig. 6. a, Dye injected into pyloric region of stomach. The staining of nodes is limited correspondingly to the right half of the stomach. The area of injection is indicated by heavy diagonal lines. Arrows indicate nodes containing malignant cells. In Figure 6b, the injection has been limited to the fundus of the stomach. The staining of nodes is correspondingly limited to the left half of the stomach.

to receive lymph from that area of the stomach. There are, however, exceptions to this. For example, in one of our cases in which the right upper quadrant of the anterior wall was injected, only the subpyloric nodes were stained. In several other instances, injection of the same area resulted in staining of the nodes in the gastrohepatic ligament as one might expect. Whether this inconstancy is due to variations in the natural patterns in different individuals or is due to blockage of pathways in some cases, we are unable to say. With our present method of injecting the muscularis along both curvatures, all or most of the regional groups of nodes receive the dye, and variations in lymphatic patterns become a negligible factor from a clinical standpoint.

There are several pathologic factors which may interfere with passage of the dye from the site of injection to the regional nodes. Some of the cases in which injections have been made with our present technique have failed to show any gross staining of the nodes, and in other cases only two or three nodes have been stained. It is our opinion that these failures have been due to pathologic changes which interfered with the passage of the dye to the nodes. One of the causes of the interference is the blockage of lymph nodes and lymphatic pathways with cancer. The cases falling into this group of failures have had gross widespread involvement of the lymphatics by cancer tissue and have not been considered resectable. In 2 instances nodes with partial replacement by cancer became stained in the portion not grossly involved with cancer (Fig. 1). This seems to indicate that considerable malignant involvement is necessary to prevent the uptake of the dye. This interference does not lessen the usefulness of the method, since nodes which are grossly involved with cancer are usually easily identified by their firmness and color. Several

failures have occurred in the cases of benign gastric ulcer in which the dye was injected in the region of the ulcer before the diagnosis of benignancy was established. In these cases the nodes either failed entirely to show gross staining, or the staining was limited to not more than several nodes near the site of injection. Braithwaite reported a similar experience in his investigations with inflammatory lesions and considered it to be due to obstruction to the flow of lymph induced by the acute inflammatory changes. This appears to be a reasonable explanation. This interference does not weigh seriously against the use of the procedure in malignancy since cancerous lesions are usually not associated with extensive acute inflammation.

A definite handicap in the procedure is the limited time permitted the surgeon for the observation of the uptake of the dye. Although a satisfactory radical total or subtotal gastrectomy requires several hours for its performance, most of the lymphatic pathways have been divided in the first hour or two of the operation. We know from studies in other situations, in which the dye has been injected the day before surgery that there is much more extensive and intensive staining after 24 hours than there is after 1 hour. Although pontamine sky blue has shown a superiority over the other dyes we have used in respect to the intensity and rapidity of the staining of the nodes, it is possible that still other dyes or other techniques will give better results than we have obtained thus far. At the present time we are experimenting with the addition of hyaluronidase to the dye with the thought that the diffusing properties of the hyaluronidase will accelerate the passage of the dye to the lymph nodes. In the several cases in which it has been used, there has been a speedier and more widespread staining of the nodes than occurred in most of the cases in which the dye alone was used.

It must be apparent that the procedure we have described is by no means perfected. Yet we have already found it so useful for the identification and removal of obscure nodes in the performance of radical gastrectomy, as well as in radical operations against cancer in other situations, that we have adopted it in our clinic as a routine procedure in the surgical treatment of those types of cancer in which spread occurs chiefly by way of the lymphatics.

SUMMARY

While there has been definite progress in the early recognition and management of gastric carcinoma, the knowledge of the manifestations of gastric carcinoma has not been fully utilized as it relates to the spread of cancer by way of the lymphatics. The numerous anastomoses of the lymphatic channels in the gastric wall make it possible for carcinoma to spread to any part of the stomach or to any of the nodes draining the stomach. Accordingly, one should logically remove all of the stomach and all of its accessible regional lymph nodes in treating the disease surgically. Although this can be accomplished by radical total gastrectomy, the small size of the nodes and the similarity of their color and consistency to that of the tissues in which they are enmeshed, and in many instances the inadequacy of the exposure, makes their removal difficult or impossible.

To accomplish the more thorough eradication of the regional lymph nodes of the stomach we have developed a method of staining them in vivo during surgery in order to make them more easily identified. A solution of pontamine sky blue, a bright blue staining dye, is injected into the wall of the stomach and is quickly taken up by the regional lymph nodes, imparting to them a blue color which makes them readily identifiable. With this procedure, nodes which would ordinarily be overlooked, because of their remote position or their resemblance to the surrounding tissues, stand out clearly for removal.

Pontamine sky blue in a 2 per cent aqueous solution has been found to be the most satisfactory of the dyes we have experimented with for this purpose. It is taken up more or less specifically by the nodes and stains them sufficiently to make them easily distinguished from the surrounding tissues during the course of the operation. Pharmacological tests have shown the dye to be nontoxic.

We have been able to demonstrate stained nodes along the course of all of the major

vessels which supply the stomach. Some of these, particularly the nodes in the region of the celiac axis and the lower esophagus, would probably have been overlooked had they not been stained by the dye.

We regard the staining of the nodes during operation as a means of more nearly approaching the ideal of adequate extirpation of the regional lymphatics in the surgical attack on carcinoma of the stomach. Investigations with the use of the dye are now under way in other viscera in which the spread of cancer is chiefly by way of the lymphatics. Changes are continually being made to improve the technique, but the method has already proved itself to be so useful that we have adopted it as a routine procedure in conjunction with the surgical attack on cancer showing a predilection for lymphatic extension.

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ARTERIAL HOMOGRAFTS

I. The Fate of Preserved Aortic Grafts in the Dog

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THE fact that fresh and preserved arterial homografts properly transplanted may be expected to function indefinitely was demonstrated experimentally over 40 years ago by Carrel and Guthrie. Largely because of technical pitfalls, however, arterial homografts in the human have never been extensively used. The need for an effective method for bridging a gap in major blood vessels was brought into sharp focus during the recent war, and current advances in the field of vascular surgery have continued to stimulate research on this problem. It has become increasingly apparent that vein-lined tubes and plastic or metal conduits are not a satisfactory solution, and since the war renewed interest has been aroused in the potentialities of the arterial homograft.

It was our purpose in this study to investigate by histological methods the fate of stored aortic homografts in the dog, and to evaluate the effect of the duration of storage upon the biological and functional properties of the transplanted vessel.

METHOD OF STORAGE OF GRAFTS

If a blood vessel "bank" is to be practical for widespread use in either civilian or military hospitals, a method of storage must be devised which is simple and requires little or no specialized or complicated equipment or solutions. For this reason, we began by using as a storage medium commercially obtained sterile Ringer's solution to which was added 10 per cent by volume freshly prepared sterile dog serum. This solution proved to be quite successful, and grafts so stored would remain in an excellent state of preservation for periods up to 6 months. At first penicillin and streptomycin were added, but in the later phases of our work we found this to be unnecessary if careful sterile precautions were observed in the preparation of the solution. We had no instance of known bacterial contamination occur in our laboratory.

The entire descending aorta from just beyond the arch to just above the bifurcation was removed under sterile precautions within 1 to 4 hours after death of the donor animal. Each efferent artery was carefully ligated by a simple tie of No. 000 silk as close to the wall of the aorta as possible. The entire artery was then placed in a sterile Mason fruit jar containing 450 cubic centimeters of the storage solution, which was tightly stoppered, and kept in a common electric refrigerator at a temperature of 3 to 8 degrees C. By observing care, this vessel could be used serially for several transplants replacing the vessel into the original bottle between implantations.

Pierce and his co-workers have recently reported their careful studies on various methods for the storage of vascular segments. They concluded that the use of a balanced salt solution containing 10 per cent plasma in stoppered bottles maintained at a temperature of 6 degrees to 11 degrees was the most satisfactory method studied. We believe, however, that the carefully evolved but complex formula for buffered salt solution recommended by Pierce is not necessary, and that commercial Ringer's solution is quite adequate.

Our method, which proved to be eminently satisfactory, requires no agents or materials not available in any civilian or military hospital, up to and including the field hospital.

FACTORS OF IMPORTANCE IN THE SUCCESSFUL TRANSPLANTATION OF STORED HOMOGRAFTS

Gross and his co-workers have stressed three factors which might influence the success or

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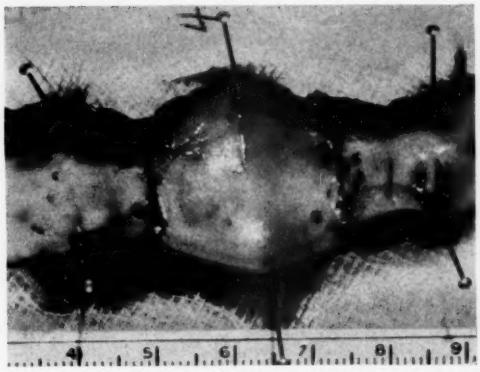

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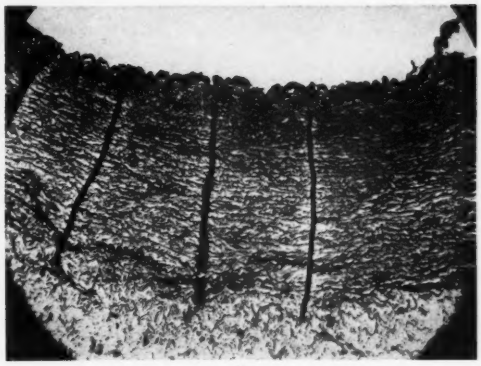


d

Fig. 1.[1] a, The graft stored 14 days has been in place for 3 days. b, At the suture line the tiny wedge-shaped thrombus has formed. c, The graft shows the absence of intima, essentially normal appearing media and acute inflammation in the adventitia. d, The elastic tissue appears to be normal.

failure of an arterial graft: (1) the viability of the vessel at the time of implantation; (2) the degree of immunological reaction between the host and the graft; and (3) the technique employed in making the anastomosis.

Insofar as the immediate (i.e. up to 1 year) *functional* result of arterial homografts in the dog is concerned, we believe the last named factor is the one of prime importance and the first two are of minor importance. The "viability" of the vessel will be discussed at some length in the following section of this report; the degree of immunological reaction which may be great in heterogenous transplants, has never appeared to have been of sufficient degree in our experience with homogenous transplants to jeopardize the survival of the graft. The immunological factors relating to nonautogenous grafts comprise a subject worthy of extensive investigation. However, as far as the *functional* success of the experimental homogenous arterial transplant is concerned, this has not appeared to be a decisive factor.

Technical aspects of the actual implantation of the vessel, on the other hand, appear to be of paramount importance. The well-established techniques of arterial anastomosis must, of course, be carefully observed. Rigid asepsis, delicacy in the handling of tissue,

[1]In all the figures in this paper, a is a photograph of the gross specimen, opened in the axis of the vessel, and viewed from the intimal side; b is a photomicrograph of the anastomosis (hematoxylin and eosin stain) with the graft always on the right and the host aorta on the left; c is a photomicrograph of the graft (hematoxylin and eosin stain); and d is the same section as c but with elastic tissue stain. All magnifications are × 45.

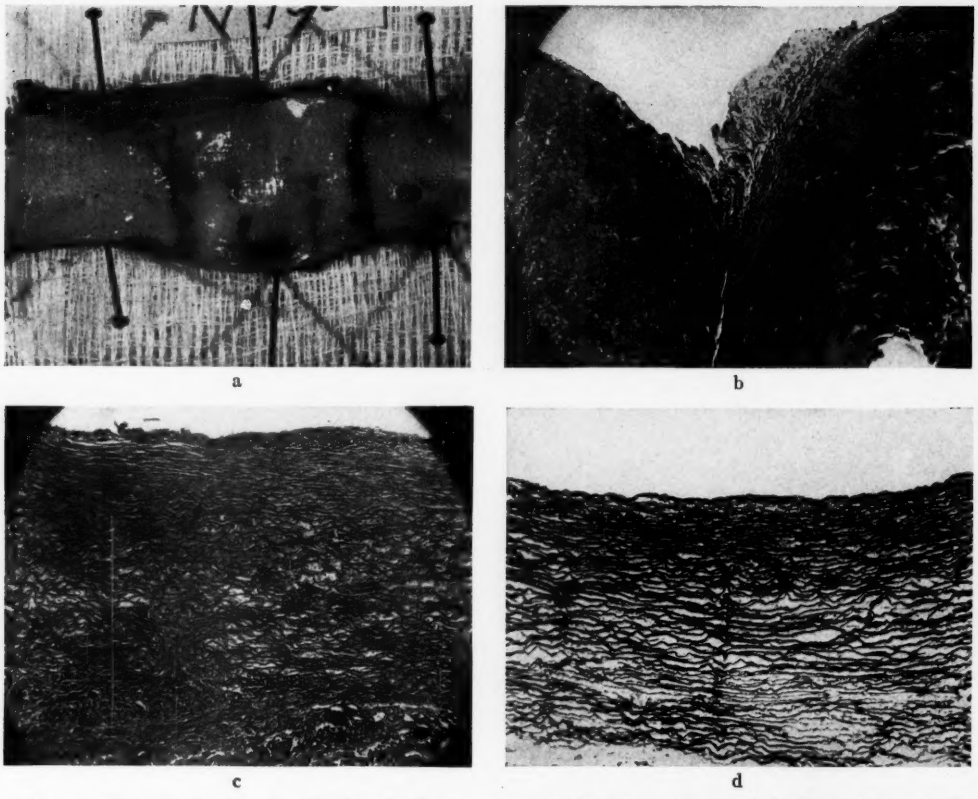


Fig. 2. a, The graft stored 21 days has been in place 14 days. b, The wedge-shaped thrombus shows invasion by fibroblasts and is beginning to extend down along the internal surface of the graft. c, Only a few of the smooth muscle cells of the media remain in this specimen. On the inner surface is a very thin plaque-like thrombus. The adventitia is now formed of granulation tissue. d, The elastic tissue appears normal.

avoidance of desiccation, the use of fine atraumatic needles with fine silk, the careful removal of the adventitia, and the avoidance of too large or too small a cuff are all matters of importance. We routinely used a series of continuous everting mattress sutures resulting in an intima-to-intima closure; other types of suture for effecting anastomosis may be equally effective (5).

The use of grafts, however, brings up other considerations than merely the technique of anastomosis. Of supreme importance in our experience is the size or diameter of the graft in relation to the diameter of the host vessel. The aorta when it is removed tends to contract somewhat. There does not appear to be further shrinkage during the time of storage. The capacity for distention remains as a function of the vessel, and upon being subjected to intraluminal pressure when implanted in the host will stretch to its previous in vivo diameter.

The creation of a vessel in continuity of uniform diameter under the hemodynamic conditions of blood flood is a law of vascular transplantation if uniformly successful results are to be expected. If the graft is allowed to exceed in diameter the host vessel, an aneurysm-like bulging occurs which results in turbulence and eddy currents in the flow of blood through the irregular channel. Intravascular thrombosis is favored, and clots may form usually

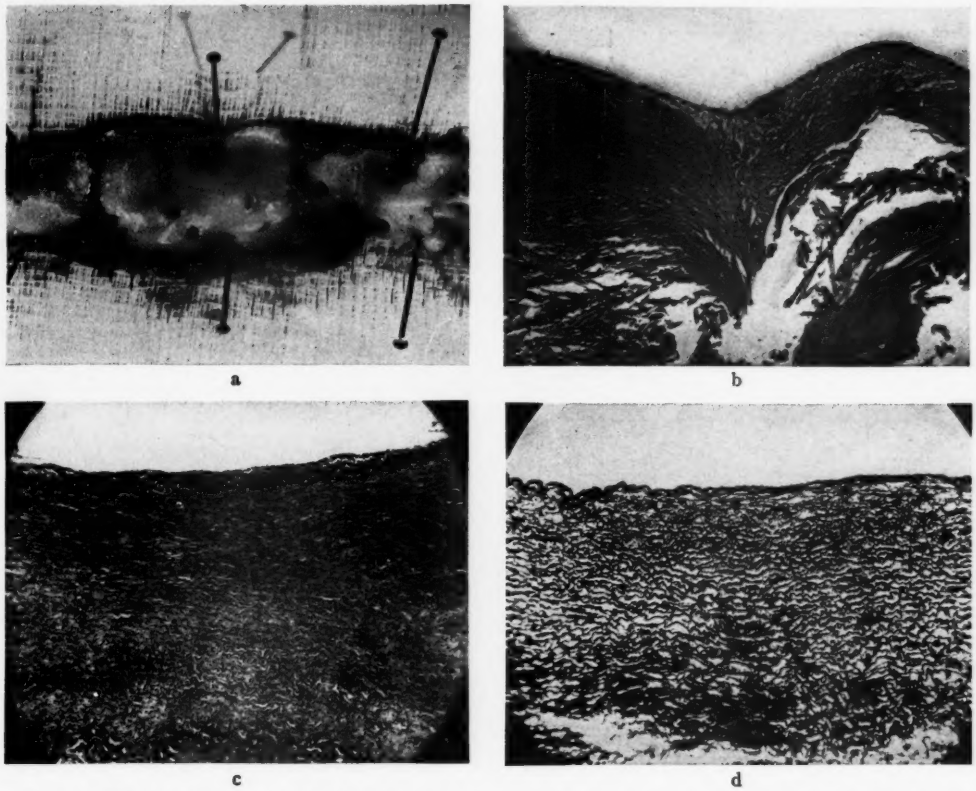


Fig. 3. a, The graft stored 10 days has been in place for 30 days. b, The wedge-shaped thrombus at the suture line has become further organized and has extended beyond the field down the internal side of the graft. Endothelial-like cells seem to line its surface. c, In this graft, smooth muscle survival in the media is very abundant. The adventitia is now composed of dense scar tissue. d, The elastic fiber pattern is relatively unchanged.

just distal to the proximal anastomosis gradually extending both distally and proximally until the lumen is obstructed and its value as a conduit ceases. Occasionally, degenerative changes in the graft occur under these conditions, with breakdown of tissue and secondary hemorrhage.

In choosing a suitable section of the stored aorta for implantation therefore, a segment should be selected which is slightly smaller in diameter than that of the normally pulsating host aorta. Under no circumstances is it wise to use a segment which is slightly or definitely larger than the host vessel. Care must then be taken to turn up as small a cuff as possible in order to avoid constriction at the suture line. In the early phase of our work the importance of this factor was not recognized, and no particular care was exercised in the choice of the graft for size, with the result that in the first few experiments thrombosis or hemorrhage supervened in over half of the animals. After realization of the phenomena involved, 36 aortic homografts have been performed with only 4 failures irrespective of the duration of storage of the graft.

EFFECT OF DURATION OF STORAGE UPON THE FUNCTIONAL SUCCESS OF THE HOMOGRAFT

Gross and his co-workers (2, 4) studied the effect of the duration of storage upon the "viability" of the blood vessel by tissue cul-

TABLE I.—EXPERIMENTAL AORTIC HOMOGRAFTS

Dog No.	Duration storage of graft days	Duration in host before sacrifice days	Results	Pictured in report
			Series A	
49-64	7	5	Successful graft; microscopic study	
48-270	8	240	Successful graft; microscopic study	Fig. 6
49-3	8	7	Successful graft; microscopic study	
49-109	8	45	Successful graft; microscopic study	
48-338	8	120	Successful graft; microscopic study	Fig. 5
48-351	10	30	Successful graft; microscopic study	Fig. 3
49-122	10	3	Died; rupture proximal suture line (graft too big)	
49-84	14	3	Successful graft; microscopic study	Fig. 1
48-344	15	2	Successful graft; died of intussusception	
49-77	17	1	Successful graft; microscopic study	
49-136	21	14	Successful graft; microscopic study	Fig. 2
49-89	22	90	Successful graft; (spec. lost down sink intact)	
49-19	29	21	Successful graft; microscopic study	
48-332	38	180	Successful graft; microscopic study	
48-219	40	60	Successful graft; microscopic study	Fig. 4
48-339	40	150	Successful graft; microscopic study	
			Series B	
49-143	45	30	Successful graft; microscopic study	
49-137	45	60	Successful graft; no photo obtained	
48-358	52	120	Successful graft; microscopic study	
48-357	56	150	Successful graft; microscopic study	
48-299	58		Successful graft, dog still living (transplanted January 19, 1949)	
49-21	59	7	Successful graft; died of intussusception; microscopic study	
49-150	59	60	Successful graft; microscopic study	
49-2	60	18	Successful graft; microscopic study	
49-4	64	180	Successful graft; microscopic study	Fig. 7
48-233	65		Successful graft; dog still living (transplanted January 26, 1949)	
49-15	65	220	Successful graft; microscopic study	
48-232	70		Successful graft; dog still living (transplanted January 18, 1949)	
48-110	70	90	Successful graft; microscopic study	
49-16	71	7	Died; rupture of suture line	
49-244	76	2	Died; rupture and thrombosis	
49-26	81		Successful graft; dog still living (transplanted February 11, 1949)	
49-23	84	4	Died; thrombosis, microscopic study	
49-57	121	42	Successful graft; animal killed in fight, microscopic study	
49-115	180	75	Successful graft; microscopic study	Fig. 8

ture methods. They found that "viability" as measured by fibroblastic proliferation in tissue culture media was enhanced by the storage of a large segment of vessel and by the use of an airtight stopper on the storage bottle. Under these conditions, vessels stored in balanced salt solution with 10 per cent serum showed a high percentage of fibroblast viability up to 37 days. Thereafter, the percentage of such viability appeared to decrease. Their series of ex-

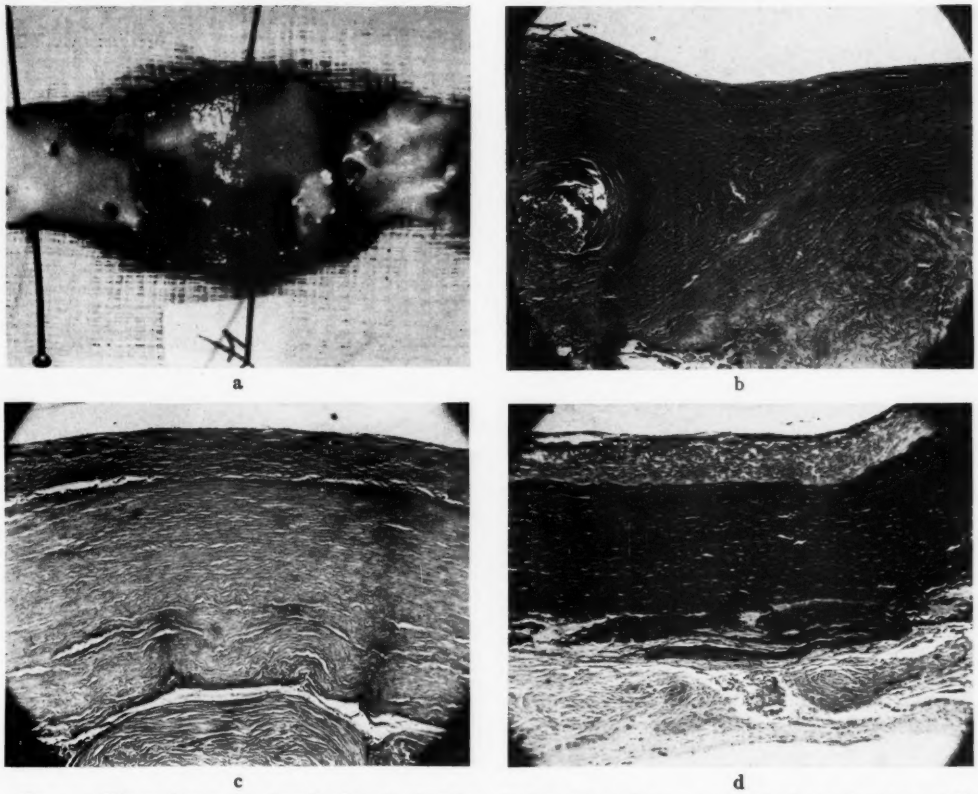
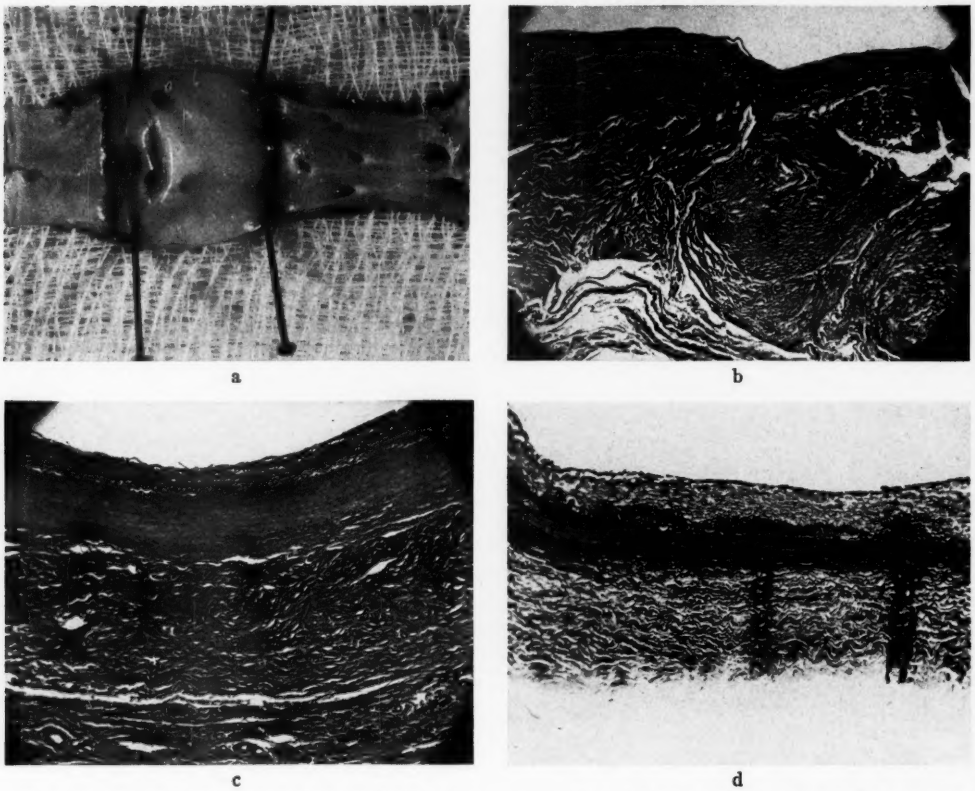


Fig. 4. a, The graft stored 40 days has been in place for 60 days. This graft shows more extensive surface thrombosis than is usual. b, At the suture line, the continued organization and differentiation of the wedge thrombus has resulted in a fibrocellular layer which smooths the contour of the lumen. c, The fibrocellular layer which grows in from the ends now covers the internal surface of the graft. In this specimen, no smooth muscle cells are seen in the media. The adventitia is becoming hyalinized. d, The elastic fibers appear very dense, possibly because with the loss of smooth muscle cells the total thickness of the media is diminished and the elastic fibers are more compact.

periments with storage of 50 days or more was quite small (3 observations) and it is possible that fibroblast viability may occasionally persist for even longer periods of time. However, in their experimental transplantations, 2 grafts stored longer than 50 days failed to function and became thrombosed. They conclude that a graft is more apt to be successful if it is "viable" when transplanted.

Our experience has led us to believe that the immediate success of the properly transplanted graft is not materially affected by the duration of storage, at least for periods up to 6 months. A series of aortic grafts stored from 40 to 180 days were implanted and allowed to remain in the host for various lengths of time before sacrificing the animal for histologic examination. Nineteen such transplantations were performed, with only 3 failures from thrombosis or hemorrhage. At the present time, a graft stored 70 days has been functioning for a period of 10 months in an animal apparently in perfect health. Table I is a summary of the pertinent data of our series of aortic homografts.

To say that the duration of storage has little apparent effect on the immediate success of the homogenous arterial transplant is not to say that it may not have a significant effect upon the ultimate outcome. Histologic evi-



a b c d

Fig. 5. a, The graft stored 8 days has been in place for 120 days. b, At the suture line the fibrocellular layer has smoothed the contour of the lumen. The surface layer of endothelium appears quite definite. Differentiation of the fibrocellular layer is apparent. c, The media is thin and compact. No cells are visible. The adventitia is a thick, dense, hyalinized scar. d, The elastic fibers appear less dense and the layer is thinner. It is apparent that new elastic fibers have been formed in the layer of fibrocellular tissue.

dence suggests that there are differences in the cellular structure of the resultant vessel between grafts stored for short periods of time and those stored for long periods. The "old" grafts demonstrate more pronounced degenerative changes earlier than those seen in "young" grafts. The nature of these changes is described in more detail in the following section of this paper, but we wish to emphasize that, although the immediate functional results using "old" grafts is equivalent to those obtained using "young" ones, our period of observation at this time (10 months) is too short to allow opinion as to the ultimate fate of these grafts, and there is reason to believe that "young" grafts (i.e. less than 40 days storage) may ultimately prove to be more durable.

HISTOLOGIC EVIDENCE ON THE FATE OF THE ARTERIAL HOMOGRAFT

In our experiments, we used the abdominal aorta just above the inferior mesenteric artery as the recipient area. The aorta was mobilized for a distance of about 4 centimeters, divided between special broad-bladed noncrushing clamps, and the ends allowed to contract. Into the gap a graft 2 centimeters in length was placed. This graft was carefully matched for size as described, and therefore might be taken

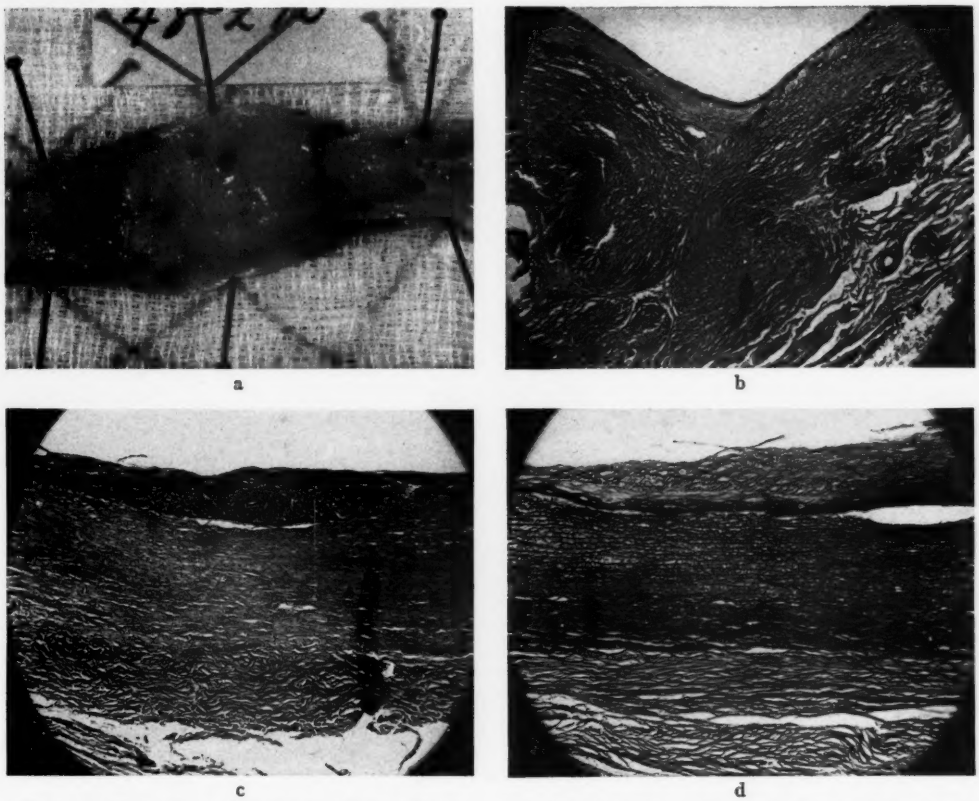


Fig. 6. a, The graft stored 8 days has been in place for 240 days. b, The anastomosis is firmly healed. c, The fibrocellular layer shows further differentiation and some degenerative changes. There is noticeable a spotty deposition of calcium throughout the layer and there are some smooth muscle cells visible in the media. d, The basal portion of the fibrocellular layer contains many elastic fibers. The elastic tissue of the media shows relatively normal architecture although the fibers are somewhat thin.

from the thoracic end of the donor aorta or the abdominal end, as the host vessel demanded. There are some minor histologic differences between the thoracic and the abdominal aorta in dogs relating chiefly to the thickness of the media and the abundance of elastic tissue, both of which are greater at the thoracic end. This factor introduced some minor quantitative variations in the resultant vessels but appeared to have no qualitative effect.

We have not thoroughly investigated what influence the length of the graft has on the ultimate survial. A few pilot experiments led us to believe that longer grafts survive and function equally as well as short ones and this was corroborated by a recent clinical experience in which one of us (H.S.) successfully resected a mycotic aneurysm of the thoracic aorta in a 17 year old boy and restored continuity of the vessel by the use of a stored graft 8 centimeters in length. The histologic data presented in this report, however, are all derived from transplants approximately 2 centimeters long.

Since the fate of the 3 layers of the aortic graft is apparently different, it seems convenient to describe them separately. The course of events is reconstructed from serial observations made on grafts which had been allowed to remain in the host from 1 to 240

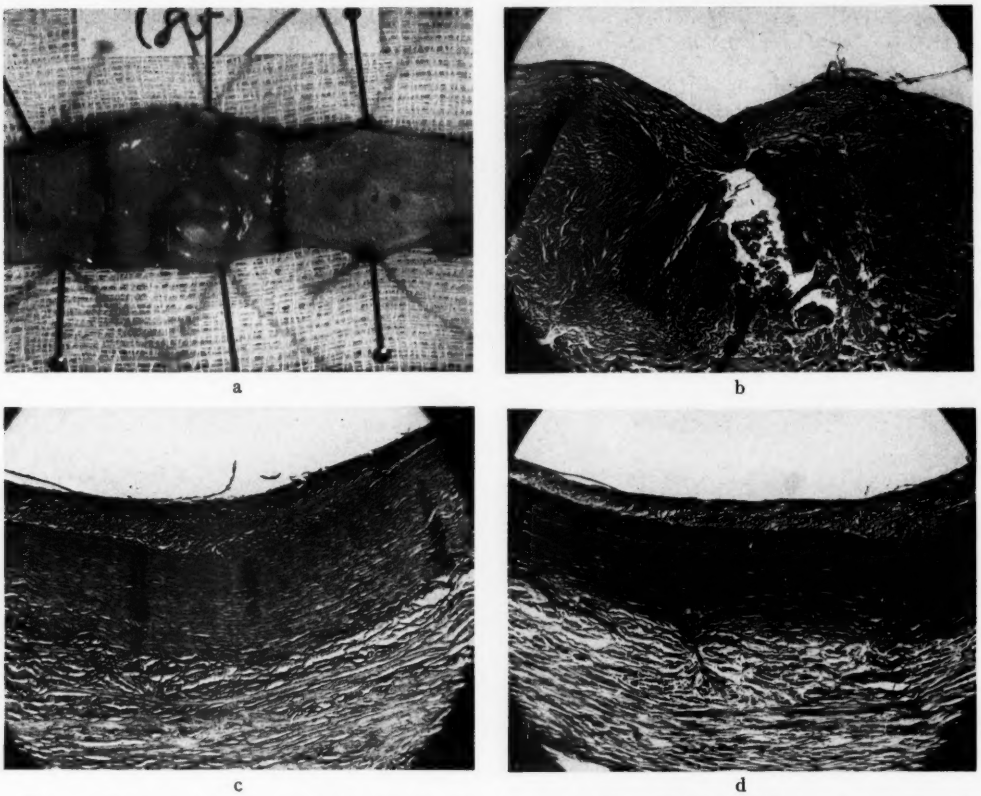


Fig. 7. a, The graft stored 64 days was in place for 180 days. A large calcium plaque is visible in the center of the graft. b, The suture line is similar to those seen with younger grafts. c, The fibrocellular layer is well differentiated and is sprinkled with calcium. No cells are visible in the media. d, The elastic tissue is dense and compressed.

days. The fate of "young" grafts stored from 8 to 40 days is described first.

Grafts stored less than 40 days. 1. The adventitia. Within 24 hours there is evidence of an acute inflammatory reaction on the part of the host evidenced by edema, fibrin deposition, extravasation of red blood cells, and infiltration of polymorphonuclear neutrophiles. This reaction reaches its height on about the third to fifth day. Degeneration of the donor fibroblasts in the adventitial layer is apparently extensive. Thereafter, healing begins by the infiltration of lymphocytes and capillary buds and fibroblasts. This granulation tissue gradually becomes more fibrous and eventually, by the end of the second month, quite collagenous. This whole process does not appear to differ in any significant way from the usual reponse to inflammation and degeneration, namely, healing by formation of scar tissue. Eosinophiles and plasma cells are not in evidence. This scar, for the first 3 months, may be much thicker than the original layer, but gradually thins out until by the sixth month it approximates the thickness of the original layer.

Thus, the adventitia of the donor vessel apparently degenerates and is entirely replaced by scar formation from the host. By the end of the second month, or perhaps earlier, it appears to be capable of contributing strength to the grafted segment.

2. The intima. At the end of 24 hours no visible trace of the intima of the donor vessel

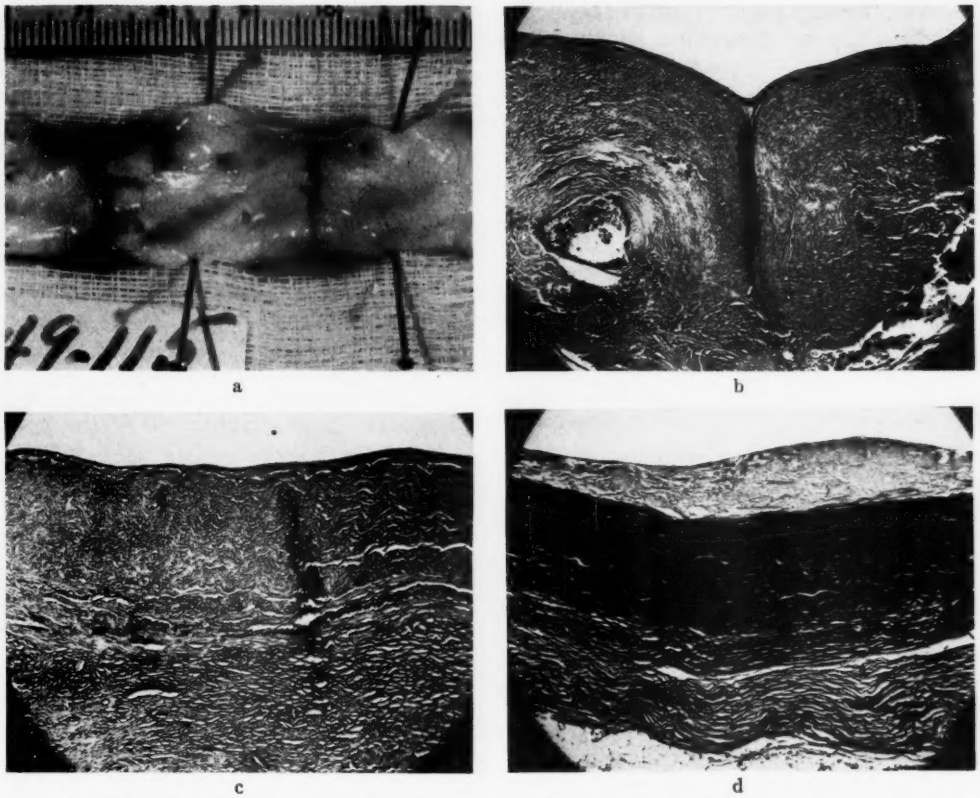


Fig. 8. a, The graft stored 180 days was in place for 75 days. b, The anastomosis is well healed. The fibrocellular layer is thin in this section, yet in other areas, as seen in d, is much thicker. c, The media shows no survival of smooth muscle cells. There is diffuse and patchy deposition of calcium throughout the media of the stained section which does not show well in this black and white photomicrograph. d, The elastic tissue appears very dense and compressed. It apparently has remained almost totally intact.

remains. The luminal surface is apparently formed by the internal elastic membrane of the media. There is no evidence of inflammatory reaction; occasionally patchy areas of very thin thrombi occur on the internal elastic membrane. A tiny wedge-shaped ring thrombus appears in the angle where the graft was everted for anastomosis. About the seventh day a growth of fibroblasts appears in this tiny thrombus, cells apparently derived from the media of the host, although perhaps from the intima. From these cells a pannus-like growth progresses from each end of the graft centrally forming a fibrocellular layer which eventually, usually by the third month, covers the entire luminal surface. This layer is not perfectly uniform but varies in thickness from a single cell in some areas to many cells in others. It tends to obliterate the angle at the anastomosis and to smooth the luminal contour of the vessel at this point. It rarely grows onto the recipient aorta's intima for any significant distance but usually becomes fused to it at the arc of eversion. Thus, by the end of the second month, the vessel has acquired from the host a new intima, albeit somewhat thicker and irregular.

Subsequently this layer shows remarkable powers of differentiation. The surface cells tend to become flattened and resemble endo-

thelium. Immediately beneath this layer, the cells have a foamy appearance. Hyalin matrix is laid down and even new elastic fibrils are formed. By the fifth month spotty areas of calcification and some deposition of lipoids, presumably cholesterol, may be observed.

It appears, therefore, that the donor intima disappears entirely only to be replaced by a fibrocellular layer derived from the host by centripedal growth from the ends. This layer by the fifth month shows both differentiation and degeneration, and by this time may be contributing to the total strength of the grafted segment.

3. The media. There appears to be more variation in the fate of the media than in that of the 2 previously described layers, but these differences seem to be merely quantitative variations of a basic pattern. For a few days, the media looks entirely normal. About the fifth day the nuclei of the smooth muscle cells begin to disappear as if the cells were degenerating. Very little inflammatory reaction accompanies this process, which continues until about the end of the fourth week. Thereafter, no further loss of smooth muscle appears to take place. The quantitative extent of this loss varies from 100 per cent in some grafts to only an estimated 50 per cent in others. Certainly in some specimens, smooth muscle cells "take" in abundance and survive for at least 8 months. By the end of the third week a pink-staining hyalin material has appeared diffusely throughout the media. The greater the smooth muscle degeneration the greater the hyalinization. This is probably hyalin degeneration rather than the elaboration of a fibrous tissue matrix as no fibroblastic proliferation is apparent during this episode.

Meanwhile, the elastic tissue fibers survive intact and continue to show little tendency to degenerate or disappear. Because of the loss of smooth muscle cells, the total thickness of the media decreases and the elastic fibers are compressed closer together. In extreme examples the media, after 4 months, consists exclusively of densely packed elastic tissue embedded in a hyalin matrix. At the opposite extreme, where there has been good survival of smooth muscle, the elastic tissue is only moderately compressed, and the general architecture of the narrowed media appears almost normal. Plaque-like calcium deposits appear in the media by the fourth to sixth month in vessels in which smooth muscle degeneration has been extensive. In the presence of such calcium depositions, elastic fibers may become locally fragmented.

The healing between the media of the graft with that of the host at the site of anastomosis is accomplished by a thin layer of fibrous tissue. The ends remain everted, and there is no tendency for the two to flatten out and become a single layer in continuity. There is no fusion of elastic tissue between the donor and the recipient vessels.

Thus, in sharp contrast to the intima and adventitia which are replaced by the host, some or most of the media of the graft appears to survive and remains relatively intact for at least 8 months. The elastic tissue always survives and, in these "young" grafts, smooth muscle may persist in varying degrees. Calcification occurs in inverse proportion to smooth muscle survival. During the first 30 to 60 days, the strength of the graft must reside primarily in the elastic tissue of the media.

Grafts stored longer than 40 days. The chain of histological events in the adventitia and intima of transplants which have been stored longer than 40 days appears to be identical with that previously described for "younger" grafts. The media, however, differs in that there is no survival of smooth muscle cells. The smooth muscle degeneration seen in the second, third, and fourth weeks progresses to completion and the media is left as a thin layer of compact elastic tissue in a hyalin matrix. By the third or fourth month, calcium deposition is commonly seen in patchy distribution, and in these areas degeneration of elastic fibers may be evident.

It is this evidence of early significant degenerative changes in the media which should lead to caution in the use of grafts stored longer than 40 days in spite of their consistent effectiveness as conduits of blood in the months immediately following implantation. We have several living animals both with "young" and "old" grafts which we propose to follow over a period of years in an attempt to evaluate the outcome of these transplants.

SUMMARY

1. Canine arterial (aortic) homografts can be successfully stored in Ringer's solution containing 10 per cent homogenous serum in an ordinary electric refrigerator at 3 to 8 degrees C.

2. For consistent successful transplantation of aortic homografts, the proper matching in size of the donor and recipient vessels is a factor of paramount importance.

3. The duration of storage (up to 6 months) does not appear to be a significant factor governing the immediate functional success of the transplant. However, microscopic evidence suggests that degenerative changes appear earlier and are more extensive in grafts stored longer than 40 days than in those stored for a lesser period.

4. Serial microscopic studies indicate that the adventitia and the intima of the graft are totally replaced by similar layers derived from the host.

5. At least a part of the media of the graft apparently survives. The elastic tissue invariably remains for periods up to 10 months. Some smooth muscle cells in varying degree survive in grafts stored less than 40 days; no smooth muscle cells survive in grafts stored longer than 40 days.

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A NOTE ON THE USE OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) AND ESTRADIOL BENZOATE (PROGYNON B) IN THE TREATMENT OF GINGIVITIS ASSOCIATED WITH ENDOCRINE IMBALANCE

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IN 1932, Prinz described a type of gingivitis which was postulated to have a hormonal causation since it was encountered most frequently in menopausal women and in women with menstrual irregularities. Ziskin (5), Ziskin and Zegarelli (6), Burket, and Van Minden demonstrated that this type of gingivitis, termed by Prinz "chronic diffuse desquamative gingivitis," could be relieved by the administration of estradiol which served to stimulate epithelization and connective tissue formation in the involved areas.

Since the clinical findings suggestive of chronic diffuse gingivitis may at times resemble those seen in various nutritional deficiency states, blood dyscrasias, and hypersensitivities to ingested foods and drugs, it was decided to determine the efficacy of hormonal treatment in 2 patients in whom chronic gingivitis of the desquamative type had been the cause of their referral to the Nutrition Clinic of the Hillman Hospital, Birmingham, Alabama, for the study of suspected nutritional or metabolic disorders or both.

One of the patients had passed the menopause and the other had a long history of hormonal imbalance. In each, the gingivitis was of several years duration, and its initial appearance had coincided with gynecologic disturbances. Since the appearance of the gingivitis, each had been treated with large doses of vitamins as well as with local applications of gentian violet and with mouth washes of an undetermined nature. The response to these measures had been unsatisfactory, a factor which led us to believe that hormonal imbalance was fundamental in the causation of gingivitis in each case. The effects of injections of pituitary adrenocorticotropic hormone (ACTH) and estradiol benzoate (Progynon B) on the gingival lesions are summarized in the following case histories.

From the Department of Nutrition and Metabolism, Northwestern University. Northwestern University Studies in Nutrition at the Hillman Hospital, Birmingham, Alabama.

This study was supported by grants from the Birmingham Citizens Committee and the Martha Leland Sherwin Memorial Fund.

CASE 1. M. B., a 54 year old white woman, was admitted to the Nutrition Clinic in 1946 with a gingivitis of 6 years' duration. She had been advised by her physician that she had pellagra, and her chief complaints at the time of admission consisted of a sore mouth, nervousness, and weakness. Physical examination showed a lean, hump-backed, apprehensive, senile appearing woman who was undernourished and in poor health. She had a full complement of natural teeth which were free from caries. They were heavily stained and surrounded by massive accretions of subgingival and supragingival calculus. The interdental papillae were retracted, rounded at the ends, engorged, spongy, denuded, and raw red. They had a glazed appearance and bled easily following slight pressure. The gingival mucosae adjacent to the interdental papillae were similarly involved for a distance of approximately 1½ centimeters from the necks of the teeth to the mucolabial and mucobuccal folds. There was an extensive exudate around the necks of the teeth where deep periodontal pockets were observed. Fetor oris was striking.

Other pertinent physical findings included a slight tendency toward ecchymosis, considerable injection of both eyes, a tanned, pigmented, rough, dry, and scaly skin. The vaginal mucosa was very dry and probably atrophic. There were purpuric lesions about the meatus of the urethra and in the mucosae of the vulva and proximal vagina. These lesions extended for a distance of about 3 centimeters into the vagina and involved the entire circumference. There were no freely bleeding points or ulcerations.

A nutrition history taken shortly after admission suggested a borderline deficiency in vitamin C. The vitamin C plasma level was 0.107 milligram per cent. Bleeding time and coagulation time were normal. Although there was no positive clinical

evidence of scurvy, the teeth were scaled, and the patient was given 500 milligrams of ascorbic acid orally each day for a period of 1 month. The oral and vaginal lesions remained unchanged during this time. No changes occurred when 50 milligrams of rutin were given each day together with 500 milligrams of ascorbic acid for a period of 2 weeks.

A sex history obtained from this patient showed that she had attained menarche at the age of 15 years. Her menstrual periods had been regular and not unusual. Menopause appeared at the age of 43 years. From age 43 to age 52 she had had an interval amenorrhea. Since the history of the development of the gingival and vaginal lesions coincided with the period of the menopausal changes, a diagnosis of hormonal imbalance was suggested. In September 1949 she was given 10,000 rat units of estradiol benzoate by intramuscular injection each day for a period of 11 days. On the third day the patient volunteered that her mouth felt better and cleaner than it had in a long time. There were no objective signs of improvement noted. On the fifth day a diminution of the edema and hyperemia of the gingivae was observed. For the first time they did not bleed in response to pressure, and they felt less painful and more firm than they had in many years. The gingival edema and hyperemia continued to recede during the next 6 days. Stippling was observed on the ninth day. At this time it was noted that the hemorrhagic areas in the vagina had subsided entirely. The vaginal mucosa was moist, and a secretion was present at the introitus. At the end of the eleventh day the gingivae had lost their denuded appearance, were firm and free from edema and, except for a slight diffuse hyperemia in the region of the original lesions, appeared normal. Patient demanded to be discharged and injections were discontinued. When she returned 3 weeks later, the gingivae were again tender and sore, bled easily in response to slight pressure, and hyperemic and edematous areas were again present in the interdental papillae.

CASE 2. E. H., a 30 year old unmarried white woman, came to the Nutrition Clinic in 1944 with a chief complaint of a generalized stomatitis and dermatitis of 15 years' duration. In this interval she had been treated with massive doses of nicotinic acid, vitamin A, and ascorbic acid. In addition, she had received injections of arsenic, applications of gentian violet, and sponging with hydrogen peroxide followed by applications of white vaseline salve containing carbolic acid. None of these agents had provided more than temporary palliative relief.

Examination of the mouth showed that the free gum margins of the gingivae were retracted and edematous. The tips of the interdental papillae were excoriated, glazed in appearance and deep scarlet red in color. The gingival mucosa was painful, slick, hyperemic, desquamated, raw red in color, and covered with a mucus-like slime. The gingivae were engorged and bled easily and freely in response to slight pressure. The teeth were freely mobile, the tongue enlarged and fissured, the lingual papillae hypertrophied and denuded, and the buccal and palatal mucosae hyperemic and edematous. Areas of raised hypertrophied encrusted epithelium were present on lips and at angles of mouth. Similar appearing lesions involved large areas of skin of axillae, arms, abdomen, scalp, perineum, hands, and feet.

The patient had attained menarche at 12 years of age. At the age of 16, she developed intermittent amenorrhea, the intervals between menstrual periods often lasting as long as 5 or 6 months. At the age of 19, eleven months elapsed without menstruation. It was during this time that the dermatitis appeared, and that the lips and oral mucosae became swollen and denuded. Her mouth became so sore that she could partake only of bland liquid foods. The axillary and pubic hair disappeared and the head hair began to fall out. At the end of the eleventh month of amenorrhea, she had a spontaneous menstrual flow which lasted from 5 to 6 days. The oral swelling "shrunk just like it had been punctured." For the next 3 years the menstrual periods were regular; then she began having intermittent amenorrhea with intervals of 5 or 6 months between periods. The periods of amenorrhea usually coincided with periods of emotional stress. During these times the stomatitis and dermatitis became worse. Prior to admission the menstrual periods had been regular for 18 months, but the stomatitis and dermatitis had persisted. The character of the oral lesions, their failure to respond to vitamin and chemotherapy, and the gynecologic history led to a clinical impression of endocrine imbalance and chronic diffuse desquamative gingivitis.

The patient was injected 4 times a day for 12 days with ACTH administered intramuscularly. The total daily dosage was 50 milligrams for the first 5 days, 100 milligrams for the next 2 days, 80 milligrams on the eighth day, and 40 milligrams for the last 4 days, given in divided doses every 6 hours. By the sixth day the gingival swelling and hyperemia were considerably reduced. She stated that the teeth felt tighter. They were less mobile. There was little gingival bleeding in response to pressure. On the eighth day, islands of stippling appeared in the gingival mucosa. All of the involved areas in the gingival mucosae and interdental papillae were stippled by the end of the twelfth day. The tissue tone was excellent, and the gingivae did not bleed when the teeth were brushed. Starting with the fifth day, there was a decrease in the size of the areas of dermatitis affecting the axillae, scalp, abdomen, perineum, and palms. She volunteered she had more vigor and muscular strength and could think more clearly. As no more ACTH was available, the injections were discontinued at the end of the twelfth day. Within 6 days following the cessation of the administration of ACTH, axillary and pubic hair appeared for the first time in 12 years. In the succeeding 3 weeks gingival mucosae took on an angry red color, the tips of the interdental papillae became swollen and engorged and bled easily in response to pressure; tissues retained a stippled appearance.

The patient was then given daily intramuscular injections of 10,000 rat units of estradiol benzoate for a period of 12 days. By the end of the eighth day, there was a noticeable diminution in the degree of redness, engorgement, and bleeding of the gingivae and interdental papillae. During the next 4 days the patient volunteered that the gums felt better than they had in many years. At the end of the twelfth day, the gingivae were so much improved in color and tone that the only visible abnormality was an old rose color confined to the extreme tips of the interdental papillae. There was no bleeding even in response to pronounced pressure. Within 1 month following the discontinuation of injections, the gingivae became edematous, engorged, angry red in color, bled readily in response to slight pressure, and felt sore during mastication. The areas of dermatitis did not change in appearance during this period.

As has been demonstrated by this study and by those of Ziskin and Zegarelli (6), Burket, Van Minden, and Richman and Arbarbanel, the administration of estradiol in cases of chronic diffuse desquamative gingivitis associated with hormonal disturbances is effective in producing a remission of the symptoms. The reappearance of some of the gingival symptoms 3 weeks to 1 month after stopping the injections of ACTH and estradiol benzoate, and the resolution of these symptoms when the estradiol benzoate was reinstituted (Case 2), indicates that a maintenance dose of the deficient hormone is required to prevent the recurrence of the gingivitis until the endocrine balance is re-established.

The response of the gingival tissues to the administration of ACTH in Case 2 resembled that elicited by the subsequent administration of estradiol benzoate. Too little is known at the present time, however, of the physiological action of ACTH to account for the remission of the oral and dermatological lesions in this patient. Whether the ACTH acted upon the adrenal cortex to instigate the release of the adrenal gonadotropic hormone, thereby stimulating the ovary to release some estrogen, or whether the action is to be attributed to some as yet unidentified factor in the adrenal cortex, is a matter for speculation.

SUMMARY AND CONCLUSIONS

Two patients with clinical evidence of chronic diffuse desquamative gingivitis and endocrine dysfunction were treated with estradiol benzoate. One of the patients also received a series of ACTH injections. The findings were as follows:

1. The intramuscular administration of 10,000 rat units of estradiol benzoate per day for a period of 11 days was followed by a remission of the symptoms of chronic diffuse desquamative gingivitis in a 54 year old climacteric patient with evidence of ovarian hypofunction (Case 1).

2. The intramuscular administration of ACTH, in divided doses totaling 40 to 100 milligrams per day given every 6 hours for a period of 12 days, resulted in a temporary remission of many of the symptoms of chronic diffuse desquamative gingivitis in a 30 year old woman with a long history of menstrual disorders. Some of the gingival symptoms reappeared within 3 weeks after injections of ACTH were discontinued. The subsequent intramuscular administration of 10,000 rat units of estradiol benzoate per day for a period of twelve days also produced a remission of the symptoms in the gingivae of this patient (Case 2).

3. The findings indicate that a maintenance dose of an effective hormone is required until the endocrine balance can be re-established.

4. The results support the hypothesis that chronic diffuse desquamative gingivitis may be a manifestation of endocrine imbalance in climacteric patients and in women with menstrual disorders.

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CHLOROMYCETIN IN SURGICAL INFECTIONS

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CHLOROMYCETIN (chloramphenicol) is one of the promising new antibiotics in the chemotherapy of surgical infections. After its isolation by Ehrlich and associates (4) in 1947 from cultures of a newly described soil actinomycete named Streptomyces venezuelae, its crystallization and solution of its chemical formula were rapidly effected (1). It is particularly unique among antibiotic agents in being the first to be synthesized on a practical basis (2, 8). Chloromycetin is a nitrobenzene compound hitherto unknown in nature (2, 8). It is quite stable and is unaffected by boiling or autoclaving. It is relatively insoluble in water but soluble in propylene glycol, polyethylene glycol, and polypropylene glycol. Despite its relative insolubility, chloromycetin is rapidly absorbed from the gastroenteric tract and reaches effective concentrations in the blood within 30 minutes, peak concentrations within 1 to 2 hours, and gradually decreasing levels over the following 4 to 5 hours (1). After absorption, it appears in a high concentration in the urine and various body fluids including the bile, cerebral spinal fluid, peritoneal exudate, and cord blood of the newborn (5, 6).

The antibiotic spectrum of chloromycetin is wide and impressive (3, 4). It includes a large number of gram negative aerobic and anaerobic bacteria, many of the pyogenic cocci, the clostridia, and certain viruses and rickettsiae. The list of susceptible micro-organisms is shown in Table I, (9, 10, 11, 12, 13, 14).

Micro-organisms resistant to the activity include fungi, Entamoeba histolytica, some strains of Bacillus proteus, approximately one-half the strains of Pseudomonas aeruginosa, and many of the viruses.

Clinical administration and dosage. In general, the oral dose of chloromycetin used for adults in the treatment of acute and chronic infections has been 25 to 75 milligrams per kilogram of body weight given in 4 to 6 divided doses at intervals of 4 to 8 hours (7, 13, 14). In infants and children, the dosage used is somewhat higher, being 50 to 100 milligrams per kilogram per day. The rectal dose is 30 per cent more than the oral. For the treatment of acute surgical infections, the usual dose for a man weighing 150 pounds is 500 milligrams every 4 hours, or 750 milligrams every 6 hours. After the signs and symptoms of the disease have obviously been brought under control, the dose may be reduced.

Clinically, the drug has been administered chiefly by the oral route. It may be given effectively per rectum through the use of suppositories made with a water soluble base such as cocoa butter or carbowax in individuals unable to take medication by mouth, or in infants unable to swallow capsules. The lack of a suitable and nontoxic solvent has thus far made the parenteral administration of chloromycetin impractical except under unusual circumstances, since experimental work has indicated that the repeated injections of propylene and polyethylene glycols produced definite toxic effects in animals. This work has been reported elsewhere (2, 7).

Material and methods. Because of chloromycetin's antibiotic action in vitro against

TABLE I.—SUSCEPTIBLE MICRO-ORGANISMS

Escherichia coli	Streptococcus hemolyticus
Escherichia coli communis	Streptococcus nonhemolyticus
Aerobacter aerogenes	Streptococcus anaerobicus
Bacillus alcaligenes faecalis	Pneumococcus
Bacillus proteus vulgaris	Corynebacterium diphtheriae
Neisseria catarrhalis	Clostridium tetani
Pseudomonas aeruginosa (some strains)	Bacillus anthracis
Salmonella typhosis	Clostridium perfringens (welchii)
Salmonella paratyphi	Gaffkya tetragena
Salmonella enteritidis	Rickettsia prowazeki
Salmonella schottmuelleri	Rickettsia rickettsi
Shigella dysenteriae	Rickettsia orientalis
Shigella paradysenteriae	Rickettsia mooseri
Brucella abortus	Psittacosis virus
Brucella melitensis	Lymphogranuloma virus
Klebsiella pneumoniae	Atypical pneumonia virus
Hemolytic Staphylococcus aureus	
Hemolytic Staphylococcus albus	

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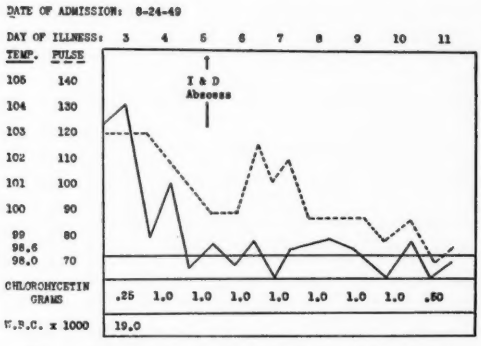

Fig. 1. M.D., white girl aged 3 years admitted to hospital with cellulitis of left arm and axillary lymphadenopathy of 3 days' duration produced by the hemolytic staphylococcus and hemolytic streptococcus. Under treatment with chloromycetin, the temperature fell to normal and cellulitis disappeared. Localized abscess developing on third day of treatment was incised and drained. I, and D, incision and drainage.

many of the gram negative and gram positive bacteria, a clinical study was started 6 months ago at the Cincinnati General Hospital in order to assess the value and limitations of this agent in a variety of surgical infections. Up to the present time, 100 patients have been treated. The cases were selected at random in an effort to test its efficacy against simple and complicated infection, and to explore therapeutic possibilities in disease heretofore unaffected by antibiotics. Obviously, the number and variety of cases studied are insufficient to draw any conclusions which would be statistically significant. However, certain clinical impressions were obtained which seemed to be valid.

The cases studied consisted of 23 staphylococcal infections, 4 aerobic streptococcal infections, 3 anaerobic streptococcal lesions, 43 mixed gram negative and gram positive bacterial infections, 8 pure gram negative bacillary lesions, one Clostridium welchii infection, and a miscellaneous group of lesions, many of which were of unknown etiology. Included in the latter were Hodgkin's disease, lymphopathia venereum, carcinoma, and blastomycosis. Emphasis was placed on studying the effect of chloromycetin on patients with mixed gram negative and gram positive bacterial infections because of the resistance of this type of infection to other forms of chemotherapy, particularly with single chemotherapeutic agents.

Whenever possible, the etiologic agents were determined and their susceptibility to chloromycetin and penicillin measured at the start of treatment and at intervals of 3 to 7 days during treatment.

The dose of chloromycetin used varied between 25 and 100 milligrams per kilogram for 24 hours, the dose being varied with the severity and stage of the infection. In general, during the acute phase of the infection, an interval of 4 hours was used until the signs and symptoms of the process were brought well under control. Thereafter, the interval was increased to 6 or 8 hours. In the 23 staphylococcal infections, the average duration of treatment was 6.7 days and the average total dose of chloromycetin was 8.6 grams. In the aerobic streptococcal infections, the average duration of treatment was 4.75 days and the average total dose 5.8 grams. In anaerobic streptococcal infections, the average duration of treatment was 18 days and the average total dose 23.7 grams. In mixed gram positive and gram negative infections, the average duration of treatment was 12.44 days and the average total dose 17.82 grams. During treatment, each case was observed to determine any beneficial effect of chloromycetin on the course of the infection and any possible toxic action on the patient.

Results. Obviously the number and variety of cases studied are insufficient to draw any conclusions which would be statistically sig-

TABLE II.—RESULTS OF CHLOROMYCETIN TREATMENT

Staphylococcal Infections		Results		
No. of cases	Type	Excellent	Good	Questionable
7	Cellulitis	5	1	1
6	Wound infection	3	2	1
7	Abscess	2	5	
1	Peritonitis		1	
1	Osteomyelitis		1	
1	Felon		1	
23		10	11	2

nificant. Many factors which always make the evaluation of a new chemotherapeutic agent difficult in surgical infections must be kept in mind. These include clinical variation of the infection in different individuals, the normal tendency of many surgical infections to heal spontaneously after operation, the variation of the host response to infection, bacterial synergism, and the simultaneous presence of other metabolic diseases, injuries, or infections which may cause the patient's death even though the infection in question is controlled by the chemotherapeutic agent.

However, on the basis of a comparison of the clinical results with chloromycetin and those obtained previously in an extensive experience with the sulfonamides, penicillin, and streptomycin, certain clinical impressions were obtained which seemed to be valid. Routine determinations of the white blood count, red blood count, hemoglobin and urine showed no evidence of suppression of the bone marrow or renal irritation.

In 23 cases of common pyogenic staphylococcal acute surgical infections such as cellulitis, infected wounds, and abscess, a beneficial result was obtained in 21 instances (Table II).

In 10 of the cases the response was excellent, consisting of prompt improvement beginning within 24 to 36 hours, return of temperature to normal within 72 hours or less, and spontaneous resolution of the process. This was particularly true of the cases of cellulitis, regardless of their extent. In the 11 cases in which the results were considered to be good,

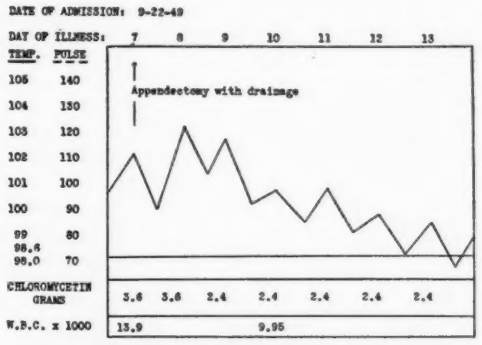

Fig. 2. M.W., a white female aged 53 years with acute perforated appendicitis with peritonitis and periappendiceal abscess, 7 days after onset. Treatment consisted of appendectomy with drainage and chloromycetin administered by rectal suppository. Dose was 60 milligrams per kilogram at start of treatment. Temperature and pulse were normal after sixth day. Wound healed without infection. Patient discharged on eighth postoperative day.

the infection usually was of longer duration and septic necrosis of tissue often occurred requiring surgical drainage (Fig. 1). The hemolytic Staphylococcus aureus was the usual pathogen in these cases. A questionable result occurred in the remaining 2 cases. In the 20 cases showing a beneficial response to chloromycetin, the hemolytic Staphylococcus aureus was found to be resistant to penicillin in vitro tests in 9 instances. In only one instance was the strain of infecting staphylococcus found to be resistant to chloromycetin and a questionable clinical response occurred in the patient infected by this organism. In the aerobic streptococcal infections, an excellent result was obtained in 2, a good result in 1, and a questionable result in 1. In the instance of a questionable result, the hemolytic streptococcus was found to be resistant to chloromycetin in the vitro test (Table III).

Of the anaerobic streptococcal infections, 1 patient with recurrent abscesses of the right breast with a burrowing sinus tract of 3 years' duration, obtained a spectacular result with chloromycetin administered orally for 17 days. There was complete disappearance of clinical evidence of the infection with cessation of discharge, disappearance of all redness, induration, and fever. In 2 patients with chronic burrowing ulcerations, 1 of the buttocks and the other of the axilla, the adminis-

TABLE III

Aerobic streptococcal infections		Results			
No. of cases	Type	Excellent	Good	Questionable	Failure
3	Cellulitis	2		1	
1	Infected wound		1		
4		2	1	1	0
Anaerobic streptococcal infections					
1	Recurrent abscess of breast.	1			
2	Burrowing ulcer.		1		1
3		1	1	0	1

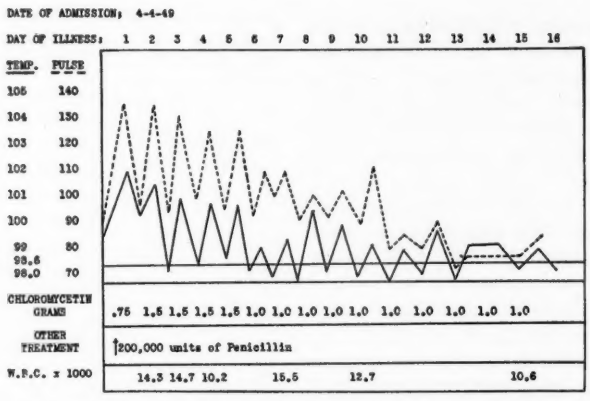

Fig. 3. L.D., colored female aged 28 years with recurrent pelvic inflammatory disease previously found to be resistant to penicillin and chloromycetin. Spontaneous resolution of infection occurred gradually during chloromycetin therapy in rather low dosage.

tration of chloromycetin produced a good result in one and a failure in the other. In both instances the treatment was accompanied by attempted surgical excision of the tracts. The anaerobic streptococcus in all 3 of these cases had become resistant to penicillin as the result of previous episodes of therapy, yet all were sensitive to chloromycetin in vitro tests.

The results of chloromycetin therapy in 9 cases of pure gram negative bacterial infections were excellent in 5, good in 2, and questionable in 2. These cases consisted of 3 patients with peritonitis or intra-abdominal abscess (Fig. 3), one with postoperative wound infection, 2 with septicemia, and 3 with typhoid infections (Table IV).

In 1 patient with peritonitis, an intra-abdominal abscess and a Bacillus pyocyaneus septicemia, a good clinical response was obtained, the blood stream being sterilized and recovery occurring after drainage of the abscess. In other patients in which Bacillus pyocyaneus was the single or co-operating etiologic agent, clinical improvement occurred in only about one-half of the cases. In peritonitis, chloromycetin appeared to be a valuable therapeutic adjunct providing the indicated surgical procedure was also carried out and providing the dose was large, being approximately 50 to 100 milligrams per kilogram per 24 hours (Fig. 2). The invasive characteristics were usually overcome in 48–72 hours, but localized infections with pus formation required surgical drainage as usual. In 1 case of pylephlebitis with peritonitis and Bacillus coli septicemia following an acute perforated appendicitis, recovery followed the use of chloromycetin and penicillin with control of the septic course, sterilization of the blood stream, and gradual return of the temperature to normal (Fig. 4).

TABLE IV

Gram negative bacterial infections		Results		
No. of cases	Type	Excellent	Good	Questionable
2	Septicemia	1	1	
3	Peritonitis	1	1	1
1	Postoperative wound infection			1
3	Typhoid	3		
9		5	2	2

The effect of chloromycetin was usually excellent or good in mixed gram positive and gram negative acute wound infections when treatment was accompanied by the indicated surgical toilet of the wound. In a few instances of rapidly spreading infections of this type, the response to chloromycetin therapy was exceedingly gratifying. However, in chronic wound infections of mixed bacterial

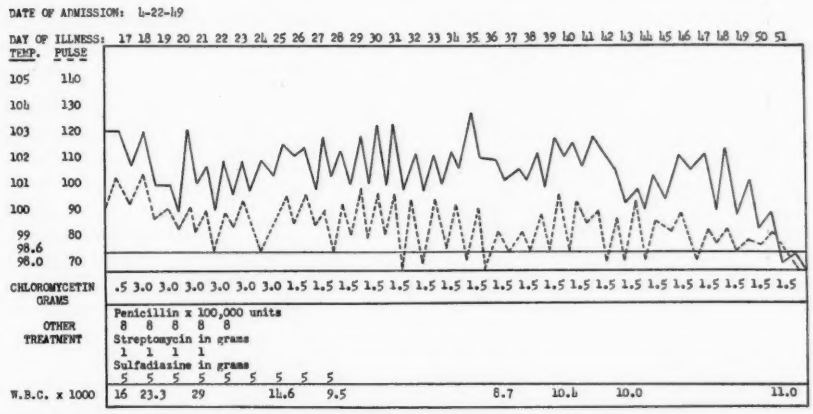

Fig. 4. L.S., white female aged 46 years with pylephlebitis and Escherichia coli septicemia complicating acute perforated appendicitis with abscess 17 days after onset. Incision and drainage had been done on seventh day of illness. Blood culture, which had become positive while patient was under treatment with penicillin, streptomycin, and sulfadiazine, became negative 24 hours after start of chloromycetin. Patient's febrile course protracted, but patient recovered.

etiology, the clinical response was less satisfactory, failures occurring more frequently (Table V). If the response was good, it was often temporary unless treatment was accompanied by operative management of the wound.

In 1 patient with a Clostridium welchii infection of a postoperative abdominal wound infection produced by Clostridium welchii, a good response was obtained in association with surgical drainage. The invasive and spreading characteristics of infection were quickly brought under control and the patient was definitely convalescing within 72 hours. Five cases of lymphopathia venereum gave variable response to chloromycetin therapy. The results were considered excellent in 2, good in 1, questionable in 1, and undetermined in 1. The questionable result occurred in a patient treated only for 8 days, with an inadequate amount of 6.75 grams. In 2 cases of Hodgkin's disease, temporary improvement occurred which lasted from 2 to 6 weeks following therapy with chloromycetin for 14 and 15 days. Exacerbation of the process occurred in both instances later, however.

In 1 case of facial blastomycosis treated for 12 days with chloromycetin, no evidence of beneficial response was detected.

Two symbiotic ulcers produced by hemolytic staphylococci and nonhemolytic anaerobic streptococci responded to chloromycetin therapy after failing to respond to other forms of chemotherapy, including penicillin (Table VI).

In 1 patient with a rapidly growing carcinoma metastatic to the abdominal wall, chloromycetin was administered. She also had a cholangitis with fever, chills, and mild icterus. An excellent response of the cholangitis was obtained, the temperature returning to normal

TABLE V

Mixed gram negative and gram positive infections		Results			
No. of cases	Type	Excellent	Good	Questionable	Failure
13	Wound infections	5	6	1	1
6	Peritonitis	2	3	1	
6	Peritonitis with intra-abdominal abscess		4	1	1 (death)
6	Soft tissue abscess		5	1	
2	Empyema		1		
1	Perinephritic abscess		1	1	
1	Pyonephrosis			1	
1	Periurethral abscess		1		
3	Sinus tract		1	1	1
1	Purulent otitis media			1	
3	Chronic osteomyelitis		2	1	
43		7	24	9	3

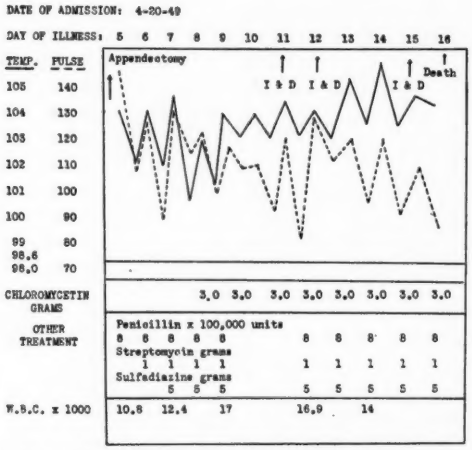

Fig. 5. B.A., a negress aged 26 years with acute perforated appendicitis with peritonitis, bilateral subphrenic abscess, pelvic abscess, and interloop abscess. Chloromycetin, penicillin, streptomycin, and sulfadiazine failed to control infection. Patient died before second subphrenic abscess could be drained.

within 48 hours and the icterus clearing. There was no effect upon the rapidly growing carcinoma.

Untoward results. There was little evidence of toxicity manifest in these patients and no serious toxic reaction in any patient. Nausea and impairment of appetite were noted in 4 cases. Malaise after the 10th day of therapy was complained of by 3 patients. This symptom, however, is extremely hard to evaluate because of its existence in infectious processes. Diarrhea occurred in 1 patient. A maculopapular cutaneous rash developed in 3 patients on the 4th and 7th day after the start of treatment. In each instance it disappeared 3 to 5 days after discontinuation of the drug. A stomatitis with brick red discoloration of the mucous membranes of the mouth and a burning sensation of the tongue and palate was noted in 2 of the patients exhibiting maculopapular cutaneous rashes.

It is significant to note that bacterial resistance of 1 or more species of bacteria to chloromycetin occurred in 11 of the 100 cases. The bacteria sensitive to chloromycetin at the start of therapy which subsequently became resistant to chloromycetin included the hemolytic Staphylococcus aureus in 3 instances, the nonhemolytic Staphylococcus aureus in 1, the nonhemolytic streptococcus in 1, the Bacillus proteus in 5, and the anaerobic streptococcus in 1.

TABLE VI

Miscellaneous		Results			
No. of cases	Type	Excellent	Good	Questionable	Failure
5	Lymphopathia venereum	2	1	2	
2	Hodgkin's disease				2
1	Blastomycosis				1
1	Cholangitis	1			
1	Clostridium welchii		1		
4	Cellulitis (Undetermined etiology)	3	1		
2	Intraperitoneal abscess		1	1	
1	Lymphadenitis	1			
1	Subacute arthritis			1	
18		7	4	4	3

The average duration of time elapsing before resistance occurred was 18.2 days, the shortest being 5 days and the longest 33 (Table VII).

DISCUSSION

An analysis of the results obtained in this study indicates that chloromycetin is a valuable addition to the field of chemotherapy for surgical infections. It has extended considerably the possibilities of effective antibiotic chemotherapy. The results obtained in the gram negative bacillary infections indicate its effectiveness in these lesions. The recovery of the 2 patients with Pseudomonas aeruginosa bacteriemia and pylephlebitis with Escherichia coli bacteriemia was particularly noteworthy.

The development of bacterial resistance to chloromycetin emphasizes the importance of not using chemotherapy with this agent indiscriminantly and without definite indication of giving it in inadequate dosage, and of timing its use with the indicated and properly executed surgery. Failure to drain abscesses before, at, or shortly after, the onset of chloromycetin may permit the development of bacterial resistance and produce infections refractory to chemotherapy.

TABLE VII.—DEVELOPMENT OF BACTERIAL RESISTANCE TO CHLOROMYCETIN DURING TREATMENT

Organism	Time
Bacillus proteus	33
Bacillus proteus	12
Bacillus proteus	33
Bacillus proteus	20
Bacillus proteus	22
Hemolytic Staphylococcus aureus	5
Hemolytic Staphylococcus aureus	18
Hemolytic Staphylococcus aureus	11
Nonhemolytic Staphylococcus aureus	13
Nonhemolytic streptococcus	13
Anaerobic streptococcus	21

There are indications that chloromycetin will be of considerable value in the treatment of a large group of mixed gram positive and gram negative bacterial infections. Lesions produced by such a mixture of organisms have always been notably resistant to chemotherapy and other forms of treatment because of the synergism of the infecting bacteria, the tendency for the production of necrosis, the development of extensive abscesses in the peritoneal and pleural cavities, the marked toxemia, and the tendency to spread progressively.

Since the great majority of the mixed infections require surgical treatment, an excellent result with prompt and spontaneous resolution of the process rarely is obtained. The results of treatment with chloromycetin and the indicated surgical procedure were good in the majority of instances, the invasive qualities of the infection being quickly overcome and the local manifestations of the infection disappearing. The presence of resistant strains, delayed diagnosis, or delayed surgical drainage may produce a questionable result or failure (Fig. 5). Whether chloromycetin can be expected to produce a favorable outcome in the majority of instances in mixed infections when used without other chemotherapeutic agents has not been determined.

Pyogenic infections produced by a gram positive cocci respond very well to chloromycetin but not quite as decisively as with penicillin. In penicillin-resistant infections produced by these organisms, the effectiveness of chloromycetin is particularly noteworthy.

As yet the antirickettsial and antivirus activity of chloromycetin has not been of much benefit in surgical practice. In lymphopathia venereum, chloromycetin holds considerable promise, particularly in the earlier cases. Considerable improvement occurred in those associated with intra-abdominal granulomas and abscesses.

SUMMARY AND CONCLUSIONS

1. Although this series as yet is too small to permit conclusions, it appears that chloromycetin is a chemotherapeutic agent of considerable value in the management of surgical infections.

2. Its low toxicity is noteworthy.

3. The effective dose for the majority of surgical infections varies between 25 and 100 milligrams per kilogram of body weight per day when given by mouth. When given by rectal suppository, the dose may be increased 30 per cent.

4. A satisfactory interval between doses of chloromycetin for treatment of severe and acute infections is 4 hours. Less severe infections or those brought under control may do well when chloromycetin is administered at intervals of 6, 8, or even 12 hours.

5. Chloromycetin is effective for both general and localized infections produced by many of the gram negative bacteria, although only one-half of the strains of pseudomonas aeruginosa are sensitive to its action.

6. Lesions produced by gram positive cocci respond well to its administration, but not as rapidly nor as decisively as to penicillin.

7. Chloromycetin is particularly valuable in the management of penicillin resistant pyogenic infections.

8. In mixed infections, chloromycetin appears to be superior to penicillin, streptomycin or sulfadiazine.

9. Bacterial resistance of some species of bacteria to chloromycetin may occur during or after treatment.

10. Surgical drainage or other operative procedures which are indicated should be done early, either during or before chemotherapy with chloromycetin to prevent the development of chloromycetin fastness.

11. The success or type of response to chloromycetin in the management of established surgical infections seems to depend largely upon the duration of the infection, early diag-

nosis, the age of the patient, susceptibility of bacterial strains to chloromycetin, the proper coordination of surgical treatment, and the presence of concomitant metabolic or other diseases.

12. The fundamental surgical principles of early treatment, rest, adequate external drainage, and general supportive treatment remain as important as ever.

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CRANIOPHARYNGIOMAS

(Pituitary Adamantinomas)

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CRANIOPHARYNGIOMAS constitute a small but important group of intracranial neoplasms. As reported in the literature, they comprise approximately 4 per cent of all intracranial neoplasms and about 30 per cent of all pituitary tumors. They are the most frequently occurring tumors of the supratentorial cavity in children (5). A variety of names has been used in the literature to describe these tumors, such as hypophyseal duct tumors, craniopharyngeal duct tumors, Rathke pouch tumors, craniobuccal cysts, suprasellar cysts, epitheliomas, interpeduncular cysts, simple squamous epitheliomas and adamantinomas.

NATURE OF STUDY

This inconstant terminology has led to confusion. In view of this, it has seemed worth while to review the whole subject of craniopharyngiomas. To this end, the pertinent literature has been examined and 100 cases of craniopharyngioma in which the clinical diagnosis was verified surgically or at necropsy at the Mayo Clinic have been studied. In the course of such study, several specific objectives have been kept in mind: (1) the embryologic development, (2) study of the pathologic features with particular reference to the microscopic appearance, (3) consideration of the clinical and diagnostic aspects of craniopharyngiomas, and (4) evaluation of the surgical and roentgen-ray treatment of these tumors.

EMBRYOLOGIC DEVELOPMENT

According to the generally accepted idea, the hypophysis arises from two outgrowths of ectoderm. One is a pouch extending upward from the roof of the primitive mouth cavity, and the other is a protrusion downward from the floor of the third ventricle, which occupies a position immediately behind the pouch of the mouth (Fig. 1, a and b). The orifice of the mouth pouch or Rathke pouch gradually contracts, and a long slender duct is formed which soon becomes solid. This is the so called craniopharyngeal duct or pituitary stalk. The mesenchymal foundation of the sphenoid bone is being laid down at this same time, and as a result there is considerable separation between the oral cavity and the brain. At about the same time, the mouth pouch comes in contact with the neural protrusion from the third ventricle and thus the pars anterior, pars intermedia and pars nervosa form. The remains of the original cavity of Rathke's pouch serve to separate the pars nervosa and the pars intermedia. Where the craniopharyngeal duct joins the remaining dilated mouth pouch, there are two lateral processes, one on each side, called the "tuberal processes," which give rise to the pars tuberalis (Fig. 2 a).

As development advances, the craniopharyngeal duct becomes attenuated and disappears. This occurs during the third month of intrauterine life. The two tuberal processes increase in size, and the tips of these turn inward beneath the median eminence of the tuber cinereum. Thus, a strong connection unites the pars tuberalis with the pars anterior along the anterior surface of the infundibulum (2) (Fig. 2 b).

From this very brief description of the development of the pars tuberalis, which is that part of the pituitary body with which we are most concerned, it is apparent that the so called craniopharyngeal duct must be considered an extremely transitory structure. There is no substantial proof that any part of it is carried over into adult life in man. The

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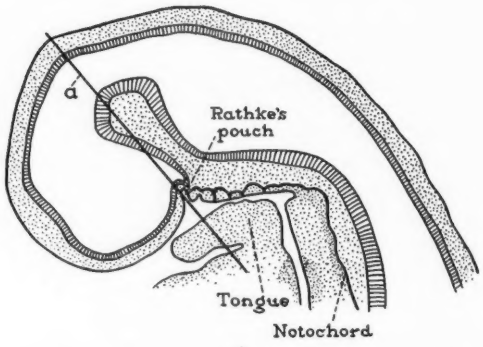

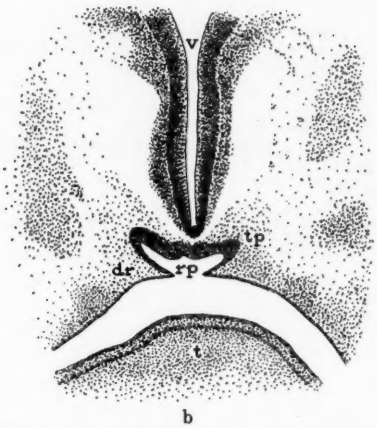

Fig. 1. a, Diagrammatic representation of an 11 millimeter human embryo: Line *a* is the level of the coronal section shown in Figure 1b; b, coronal section of an 11 millimeter human embryo, showing the close relationship of the dental ridge to Rathke's pouch: *dr* is the dental ridge, *rp* is Rathke's pouch, *t* is the tongue, *tp* is the tuberal process, and *v* is the ventricle of the brain. (Modified, with permission of the publishers, from: Tilney, Frederick, 22.)

term, "craniopharyngeal," implies that the pituitary body has a pharyngeal origin; however, the weight of evidence at present is strongly in favor of the theory that the pituitary derives not from the pharynx but from the roof of the mouth (22).

Many workers (7, 17, 21) have studied the so called epithelial rests which appear in the pituitary body and which Erdheim considered to be the tissue from which these tumors develop. All these investigators found the epithelial nests or rests along the anterior part of the infundibulum, or on the upper anterior surface of the anterior lobe of the pituitary body, in a very high percentage of cases. Most of these observers found that no groups of cells resembling squamous epithelium were found in persons less than 20 years of age. Many theories have developed as to why these embryonic rests occur in older persons. If these epithelial rests are the forerunners of craniopharyngiomas, why is it that they do not appear in the age group in which these tumors are said to be most common? Grinker has given what probably is the best explanation. He wrote that these so called epithelial rests are very slowly developing or arrested craniopharyngiomas which are developed from ordinary, but for some as yet unknown reason neoplastically inclined, pituitary cells. At any rate, the presence of adamantinomatous tumors of the hypophysis can be explained embryologically. The early intimate relationship of the pituitary plate to the dental ridge of the buccal cavity indicates the possibility of inrolling dental elements into the anlage of the tuberal processes (22) (Fig. 1b). Transition forms of epithelium are numerous in this region. It is not surprising, therefore, that the structure of adamantinomas differs from that of the epithelial remnant in the pars tuberalis.

PATHOLOGIC FEATURES

In reviewing 108 cases of craniopharyngiomas in the files of the Mayo Clinic, covering the period from 1916 to 1948, 100 were found in which the clinical diagnosis had been verified at either the surgical or the postmortem table. These tumors were fairly constant in size, shape, gross appearance, and localization. The usual size was that of a walnut, but some were as large as, or larger than, a tennis ball. One contained 325 cubic centimeters of fluid. As a rule they were spherical or ovoid. They had a smooth capsule which at times was very thin and which revealed the contained yellow or dark brown "motor-oil" fluid, cholesterin crystals, and grumous material. In some cases the tumors had developed so rapidly that they had infiltrated the surrounding tissues. Be-

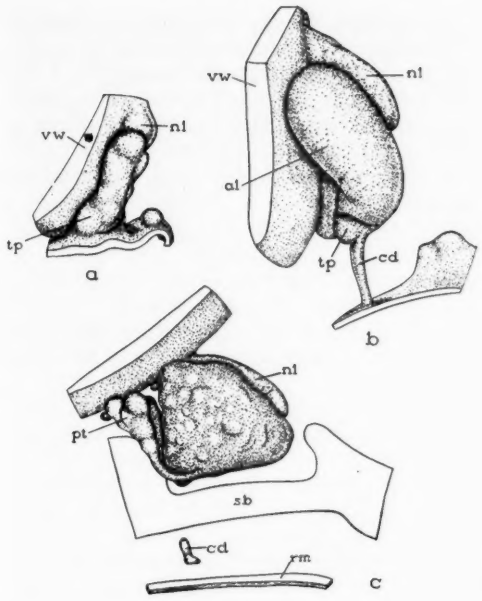

Fig. 2 a.

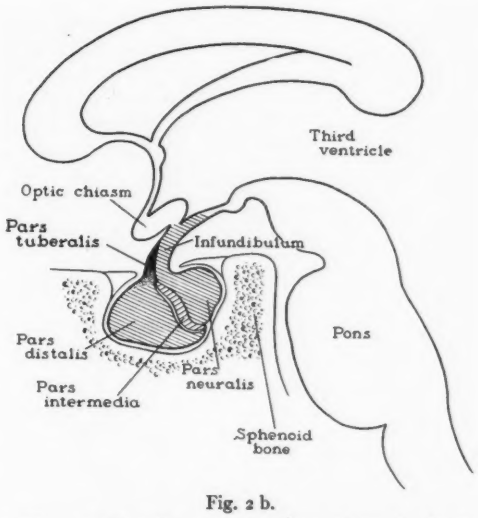

Fig. 2 b.

Fig. 2. a, Wax plate reconstructions of stages in the development of the pars tuberalis: *al*, anterior lobe of the pituitary body; *cd*, craniopharyngeal duct; *nl*, neural lobe; *pt*, pars tuberalis; *rm*, roof of the mouth; *sb*, sphenoid bone; *tp*, tuberal process; *vw*, wall of the ventricle. (Modified, with permission of the publishers, from: Atwell, W. J., 1); b, diagrammatic representation showing the location and relationships of the pars tuberalis of the pituitary body.

cause of their large size, it was impossible in most cases to determine the exact site of origin of the tumor. It was obvious, however, that if the tumor arose below the diaphragm of the sella turcica, pituitary symptoms were the first to be noted, whereas if the tumor arose above the diaphragm of the sella turcica, the adjacent optic chiasm or third ventricle was compressed and produced the initial symptoms (8).

Regardless of the site of origin, these tumors lie in intimate relationship to the optic chiasm (Fig. 3). In our series of cases there was no one tumor-chiasm relationship which occurred predominantly. The optic nerves, chiasm and tracts frequently were compressed and stretched, and on rare occasions actually were incorporated into the tumor mass. In 36 of the cases the tumor was either compressing the third ventricle or was actually invading it. In 33 cases the principal portion of the tumor was found within the sella turcica, deepening it in all directions. The pituitary body was either compressed or actually invaded in 26 of these cases. Several of the larger tumors covered almost the entire base of the brain and extended back to the pons.

A careful study was made of the microscopic sections of each tumor, with particular reference to the epithelial constituents, the connective-tissue stroma and the glial tissue reaction in the surrounding structures. This microscopic examination revealed that every lesion could be classified histopathologically as an adamantinoma. Histologically, adamantinomas are essentially epithelial growths, as might be expected on the basis of their embryonic origin. They are composed of a network of epithelial columns among which is a more or less abundant stroma, but the solid growth of the tumor often is dwarfed by the enormous cyst formation resulting from degeneration (6). As Critchley and Ironside have stated, the presence of a single row of columnar cells corresponding in structure to the embryonic ameloblasts and arranged in a palisade formation at the periphery of epithelial masses is a criterion for diagnosis of a

tumor as an adamantinoma. The epithelial columns are composed of a distinguishing cell arrangement in which three more or less distinct zones can be identified (Fig. 4a). There is a basilar layer of columnar cells lying on a definite basement membrane, an intermediate layer, and the pulp or innermost layer (Fig. 4b). The innermost cells are stellate in the older tumors, but are spindle shaped and arranged in lobules and pseudorosets in the active and rapidly growing tumors. Within the pulp of the epithelial columns epithelial whorls, similar to cell collections sometimes found near a developing tooth in man, often are seen (Fig. 4a). Intercellular bridges commonly were seen, even in the active and rapidly growing tumors. They were demonstrable in 75 of the cases. Calcification was demonstrated microscopically in 77 cases of this series (Fig. 5).

In view of the fact that several authors (3, 11, 12) have reported seeing keratohyaline granules in this type of tumor, a careful search of each case was made with this in mind, but no such granules could be found in any of these tumors. This offers a simple means of distinguishing this tumor from the epidermoids, which occur in this same area (16). Several intrasellar and suprasellar cystic tumors which have been successfully removed by the senior author and heretofore had been considered craniopharyngiomas had to be omitted from this study because of the finding of keratohyaline granules in the cells of the wall of the cyst. The histologic appearances of adamantinomas are alike, whether the lesions occur in the jaw or in the infundibular region (8). The epithelial cells of adamantinomas exhibit all the variations between stratified squamous and specialized adult ameloblasts, thus recalling the changes traversed in the normal development of the enamel organ (14). In some instances, the similarity of these tumors to the embryonic enamel organ is striking, but in others is much less so. In this series no tumor possessed any structure which could be said to resemble enamel even remotely. Nevertheless, it is probably justifiable to speak of these tumors as resembling the enamel organ, and since the term "adamantinoma" is descriptive, it probably is the best appellation for this neoplasm.

No instance of a Rathke cleft cyst, which is a dilatation of the residual cleft between the pars anterior and the pars intermedia of the pituitary body, was found in this series. These cysts are an occasional incidental finding at postmortem examination, and only rarely do they enlarge to such a size that they produce symptoms.

CLINICAL AND DIAGNOSTIC ASPECTS

Adamantinomas are common in childhood, but are by no means confined to this age period. In this series the lesions occurred in patients of the following periods: 0 to 10 years, 19 cases; 10 to 20 years, 34 cases; 20 to 30 years, 12 cases; 30 to 40 years, 15 cases; 40 to 50 years, 11 cases; 50 to 60 years, 8 cases and more than 60 years, 1 case. The youngest patient was 3 years old and the oldest was 67 years old. It is said that the sexes are about evenly affected; however, in this group of patients there were 56 males and 44 females. The duration of symptoms was extremely variable. In about half the cases it was a matter of months from the time the first symptom appeared until the patient was admitted for examination. The average length of time was 5 months. In the remaining cases, the duration of symptoms was a matter of years, 1 to 31 years, and averaging 4 years. There was 1 case in which the symptoms had been manifest for 31 years. In this series there was no relationship between the age of the patient and the duration of symptoms.

Pituitary adamantinomas produce a multitude of symptoms of greatest variety. The principal causes of such symptoms are disturbances of pituitary function, pressure involvement of the optic nerves and chiasm, hypothalamic dysfunction and hydrocephalus. The symptoms of increased intracranial pressure—that is, headache and vomiting—were the most frequent primary presenting complaints. Headache was a conspicuous feature during some phase of the clinical history in 88 cases. The character and intensity of the headaches were too variable to permit use of them as criteria for differential diagnosis. Vomiting was a prominent symptom in 41 cases; it occurred most frequently among members of the younger age groups. Cushing wrote that vomiting

in children is likely to be the predominating feature in these cases at the onset, and indeed may be regarded as a symptom of localizing nature. In our series loss of vision was the primary presenting symptom in 25 cases, and was noted subjectively during some phase of the clinical history in 82 cases.

Progressive dimness of vision was the most common mode of onset of the disease. Objectively, central vision was found to be reduced in both eyes in 73 cases and in one eye in 8 cases. The ocular findings in cases of adamantinomas are far from uniform, not only because of the variation in size and location of the tumor, but because of the varied relational anatomy of the optic pathways. The optic disks were normal in 15 cases. Papilledema was found in 28 cases; in 30 cases the disks showed pallor. Simple optic atrophy was noted in 21 cases. The appearance of the optic disks was not recorded in 6 cases. As Wagener and one of us (Love) have shown, there is a relationship between the appearance of the optic disks and the duration of the loss of vision. In the cases in which the disks were normal the duration of the loss of vision averaged 6 months. In those cases in which disks were choked, loss of vision averaged 5 months. In those cases in which there was pallor of the disks, loss of vision averaged 13 months, and in those cases in which there was simple optic atrophy, the duration of loss of vision averaged 34 months. It was difficult to generalize as to the relationship of the tumor to the condition of the disks. For the most part, it might be said that in patients with choked disks the tumor most commonly was situated behind the chiasm, and in those with simple optic atrophy the tumor was in front of the chiasm. In 57 per cent of the patients with choked disks, the third ventricle was invaded or compressed. It must be assumed, then, that increased intracranial pressure also played a part in the production of these ophthalmologic changes.

Defects in the visual fields were asymmetric, whether bitemporal or homonymous. Bitemporal defects in the visual fields occurred most commonly, being present in 41 cases. Homonymous defects were present in 23 cases; unilateral temporal defects were present in 6; bilateral central defects occurred in 4; concentric contractions were found in 2; and blindness was present in 4 cases. The visual fields were normal in 8 cases, and in 12 instances data as to examinations of the visual fields either were unobtainable or had not been recorded. Other types of involvement of cranial nerves also were noted.

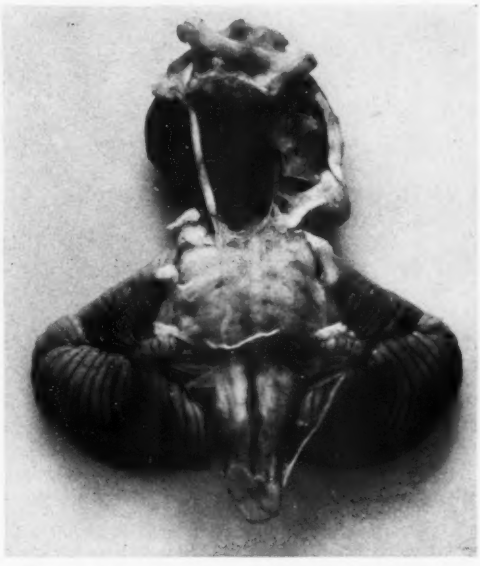

Fig. 3. A large tumor 4 by 3 by 3 centimeters, containing dark brown fluid. The left optic tract is completely transected by the anterior cerebral artery and the right optic tract is flattened. This view from below shows that the pituitary body has not been invaded or compressed.

Palsies of the third nerve were manifest in 20 cases, and unilateral facial palsy was seen in 3 cases.

Endocrine disturbances occurred in 55 of the cases of this series; in only 32 of those was the patient less than 20 years old. This refutes to some extent the claim made by some authors that endocrine disturbances are much more common in children who have craniopharyngiomas than in adolescent persons. Symptoms of hypothalamic involvement were noted during some phase of the clinical history in 31 cases. Hypopituitarism was noted in 32 of the cases and in 8 of these symptoms of both hypothalamic involvement and pituitary dysfunction were found. Depression of sexual

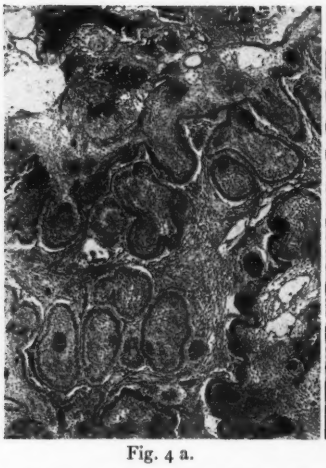

Fig. 4 a.

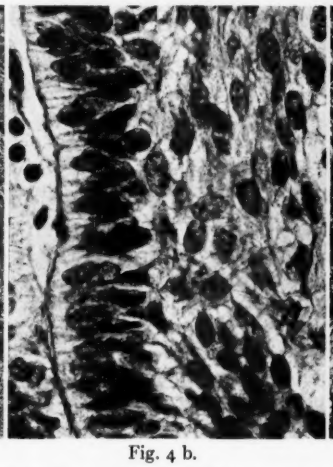

Fig. 4 b.

Fig. 5.

Fig. 4. a, Cross section of the epithelial columns which are characteristic of the cell structure in pituitary adamantinomas, showing the basilar layer of columnar cells, a stratum intermedium and a stellate layer; numerous epithelial nests also are seen (×40); b, a high power photomicrograph, showing the definite basement membrane on which the columnar cells lie as well as the intercellular bridges within the stratum intermedium and the stellate zones (×350).

Fig. 5. A large cystic cavity has formed in this tumor, with smooth regular walls composed of flattened epithelial cells. Notice the transition of the squamous cells into the stellate type of cells. Several areas of cornification and calcification also are visible (×55).

function occurred in 23 cases; it was the most common feature of endocrine disturbance. Changes in hair and skin, such as absent or scanty axillary and pubic hair, were noted in 16 cases. In 12 cases stunted skeletal development was noted; in 2 of these the condition was described as being of the Lévi-Lorain type of dwarfism. Loss of weight and emaciation were prominent signs in 12 cases. The most common manifestation of hypothalamic damage was the adiposogenital syndrome, which occurred in 13 cases. In 9 additional cases obesity was noted, and was associated with other symptoms of hypothalamic involvement.

Diabetes insipidus occurred in 19 cases. One of the patients in these 19 cases was a woman 47 years old who had suffered with varying degrees of diabetes insipidus since she was 16 years old. Approximately 2 years prior to operation polyuria and polydipsia had ceased and symptoms of anterior pituitary insufficiency had developed, indicating enlargement of the tumor mass.

A history of hypersomnia and episodes of stupor was given in 13 cases. Drowsiness was a complaint in some stage of the illness in 11 additional cases, and stupor occurred as a very late development in 12 cases. Low grade hyperthermia was noted for several months prior to examination in 4 cases.

Psychiatric changes which could be attributed to hypothalamic involvement were noted in 4 cases. In each instance the behavior was in the form of a manic state. Impairment of memory, confusion, defective judgment or retarded cerebration was noted in 15 additional cases, but probably could be attributed to involvement of the frontal lobes. It is difficult to distinguish clinically between the psychiatric changes which occur with involvement of the frontal lobes and those which sometimes accompany hypothalamic damage. Ataxia was a late symptom in 11 cases, and in 2 of the patients it was attended by definite cerebellar signs. Involvement of the frontal lobes may have been the cause of the ataxia in the other 9 patients because other cerebellar symptoms were absent (4).

Dizziness was a subjective complaint in 10 cases and tinnitus was noted in 5 instances. Convulsive seizures occurred in 4 cases. Uncinate fits were a feature in 2 cases, and in both the temporal lobes had been invaded by tumor. Signs of involvement of the pyramidal

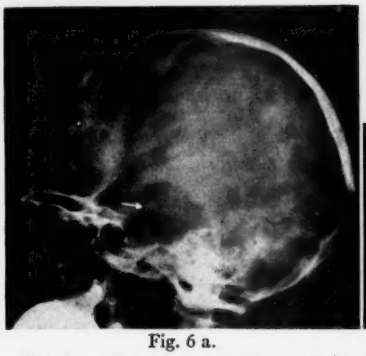

Fig. 6 a.

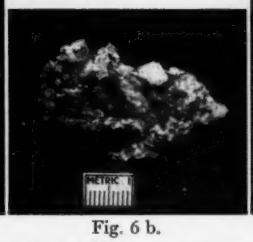

Fig. 6 b.

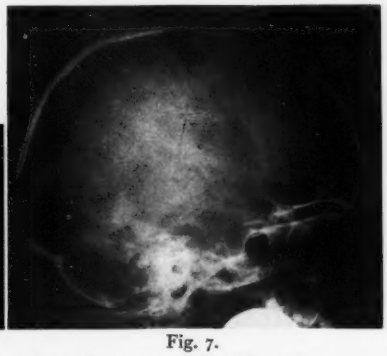

Fig. 7.

Fig. 6. a, Lateral roentgenogram of the skull of a child having a calcified suprasellar craniopharyngioma (indicated by arrow). Note the evidences of increased intracranial pressure, such as separation of the cranial sutures and increased digitation of the inner table of the skull; b, operative specimen of craniopharyngioma which was removed from the patient concerned in Figure 6, a.

Fig. 7. Postoperative lateral roentgenogram of head of same patient concerned in Figure 6, a and b. In this roentgenogram is shown the type of transfrontal flap which is employed and as well the absence of suprasellar calcification.

tract were found in 15 cases. Two patients exhibited features characteristic of paralysis agitans. According to Van Bogaert, these features probably indicate involvement of the pallidum. There was no evidence of a true thalamic syndrome in any of these cases, although 8 patients complained of various types of sensory disturbances and in 2 of these at postmortem examination the thalamus was found to have been invaded by the tumor.

Adamantinomas produce roentgenologic changes which are characteristic of both intrasellar and extrasellar tumors. Extrasellar changes indicative of increased intracranial pressure (Fig. 6a) were observed in 23 cases. The outline of the sella turcica was abnormal in 63 cases. Changes in the sella turcica indicative of an extrasellar tumor, such as a widened and flattened sella, foreshortening or erosion of the posterior clinoid processes from above, or a widened outlet, were found in 34 cases. Evidence of an intrasellar lesion was found in 29 cases.

Adamantinomas have a tendency to calcify, as was seen in microscopic study of this series, in which 77 per cent of the tumors revealed calcification. Roentgenologically, however, calcification was observed in only 56 per cent of the cases. This incidence is much lower than the 70 to 80 per cent reported by McKenzie and Sosman and others (20). The calcium shadows were suprasellar in 39 cases, intrasellar in 4 and both suprasellar and intrasellar in 13 cases. In 26 cases roentgenograms of the skull revealed no intracranial changes.

Results of routine laboratory studies at the time of hospitalization of the patient were essentially normal in these cases. Other special laboratory tests were of little value in the diagnosis.

When there is a history of headache, loss of vision and endocrine changes, the diagnosis of pituitary adamantinoma must be considered. If the symptoms occur in a person less than 20 years old, and if calcification is found roentgenologically in or above the sella turcica, the diagnosis is unequivocal. However, some of these signs and symptoms are not consistently present, and for this reason other lesions which may produce similar symptoms must be considered. Pituitary adenomas are the most common tumors occurring in the region of the sella turcica. The defects which they produce in the visual fields usually are regular, and if the adenoma is eosinophilic, symptoms of acromegaly will be present. The sella turcica in the presence of adenomas usually is symmetrically enlarged. A meningioma of the tuberculum sellae usually occurs in a patient beyond middle age, and there is a gradual development of bitemporal hemianopsia without other symptoms.

Gliomas of the optic chiasm produce a rapid loss of vision; roentgenologic examination of-

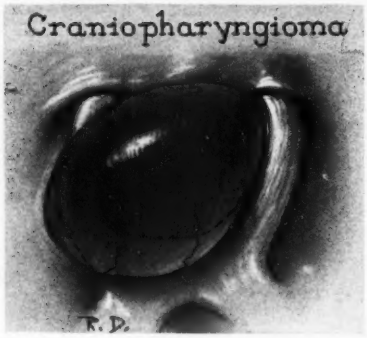

Fig. 8. Craniopharyngioma removed from a 33 year old woman who suffered progressive loss of vision (see Fig. 9) without endocrine disturbance and whose skull exhibited nothing abnormal in the roentgenograms. The cerebrospinal fluid was normal. A diagnosis of "multiple sclerosis" had been made by an experienced neurologist.

ten shows an enlarged optic foramen. Epidermoid tumors which occur in this area are classified by some authors as "craniopharyngiomas." However, epidermoid tumors unquestionably arise from misplaced rests of epithelial tissue within the leptomeninges, and are lateral to the origin of the adamantinomas. It is often impossible to distinguish them preoperatively. Recognition of them sometimes depends entirely on the presence of keratohyaline granules within the tissue (16). These granules are not seen in adamantinomas. Tumors of the third ventricle, such as teratomas, colloid cysts and gliomas must be considered. Ventriculography usually is indicated to clarify the issue in such instances. In spite of this aid, it may be impossible to make an accurate diagnosis preoperatively.

EVALUATION OF TREATMENT

Adamantinomas present one of the most difficult problems in neurosurgery. Loss of vision and increased intracranial pressure are the indications for treatment. Ideally, the treatment is complete surgical removal of the adamantinoma (Fig. 6b). This generally results in cure. However, the close anatomic relationship of vital structures which are intolerant of trauma makes successful excision extremely difficult. Aspiration of the contents of a cyst and collapse of the capsule, followed by as complete removal of the capsule as is anatomically possible, are the usual surgical procedures. Evacuation of the contents of a cyst gives only temporary relief, because rapid refilling of the cavity occurs, with return of symptoms. Ventriculography affords the only certain way of determining the exact size, position, and relationships of the tumor preoperatively. For that reason, some neurosurgeons believe that ventriculograms should be made in practically all cases (10, 19). Only rarely were they made in our series. Scarff has devised a method of intraventricular drainage in which the contents of the tumor are drained into a lateral ventricle and the cystic cavity is flushed out by cerebrospinal fluid. This supposedly permits absorption of the fluid from the tumor.

Transfrontal craniotomy (Fig. 7) is the established operative approach to tumors of the pituitary body. If the tumor cannot be exposed by subfrontal exploration of the region of the optic chiasm, transventricular approach can then be made. Some surgeons perform craniotomy on the right side, regardless of which optic nerve is most affected. Our experience has shown that the most satisfactory results are obtained when surgical removal is carried out on the side of the lower visual acuity. When diminution of vision is equal bilaterally, right transfrontal craniotomy is done, because manipulation of the right frontal lobe is less likely to produce unfavorable postoperative complications than is a similar procedure on the left. Moreover, the approach to the right side is technically easier for right-handed surgeons. It is our practice here to transfuse blood to the patient at the time the anterior fossa is explored prior to the removal of the tumor. Nitrous oxide, oxygen and ether administered by intratracheal tube is the anesthesia of choice.

Of the 100 patients with pituitary adamantinoma in our series, 2 refused surgical treatment and 2 were moribund when first seen; 96 were operated upon a total of 118 times. Transfrontal craniotomy was the approach most commonly used. It was possible to accomplish total removal of the tumor in only 15 cases. Aspiration of the contents of the capsule and partial resection of the tumor and capsule were done in 71 operations; in 10 of

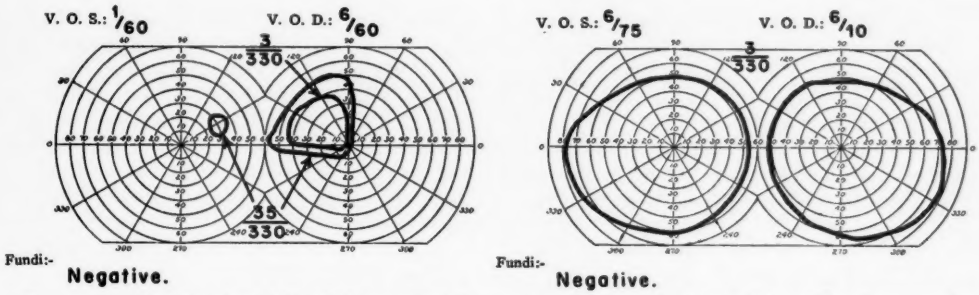

Fig. 9. Records of the visual fields which were obtained before (April 16, 1945) and after (May 10, 1945) operation on the patient with the craniopharyngioma concerned in Figure 8.

these the resection was called "extensive." Intracapsular enucleation or aspiration and curettement were done in 12 cases. In 4 cases aspiration alone was done. In 6 of the operations the tumor was not found. In 3 cases an optic nerve was cut in order better to expose the tumor mass, and in 2 of these the eye was blind before operation on the side where the nerve was sectioned. On 1 occasion it was necessary to transect the optic chiasm to get better exposure. This patient had bitemporal hemianopsia preoperatively. The anterior communicating artery was clipped and cut in 5 cases in order to secure better exposure. No loss of cerebral function was noted as a result of this procedure. In 4 of the cases the floor of the third ventricle was opened intentionally in an effort to relieve the internal hydrocephalus.

During the postoperative period, various symptoms developed as the result of postoperative edema and untoward hypothalamic reactions. Evidence of pyramidal tract impairment was noted in 18 cases, although this cleared up in some instances within the postoperative period. Marked hyperthermia occurred in 13 cases; in 6 of these it was uncontrollable and the patients died. Diabetes insipidus occurred in 9 cases in which it had been absent before operation. In 3 cases visual hallucinations were a notable feature, and mental confusion or drowsiness occurred in 12 cases. The postoperative course of 29 patients was essentially uneventful.

Funduscopic changes were noted during the postoperative period in 38 cases. Approximately 57 per cent of the patients examined showed improvement or preservation of the fields or central vision postoperatively (Figs. 8 and 9). Those patients who had had normal or choked optic disks preoperatively comprised the majority of the group showing improvement. The ophthalmologic changes which occur late after operation are of prime importance, because they often are indicative of a recurrence of the tumor. It has been possible to obtain subsequent ophthalmological data concerning 46 patients from 2 months to 13 years after dismissal from the clinic. Twenty of these patients returned for re-examination and the remaining 26 reported by letter. In this group were 33 patients in whom the fields of vision or visual acuity or both had improved or remained the same. In other words, in 72 per cent of the patients reported on or examined there was preservation or improvement in vision.

A good follow-up study of other late symptoms in this series was difficult to make, because those who got along well did not return for observation. Twenty-three patients who had had symptoms of hypopituitarism and hypothalamic disturbances prior to surgical treatment continued to have these symptoms postoperatively, and in only 3 of them were the symptoms less severe after dismissal. Thirteen patients apparently had permanent symptoms of hypopituitarism or hypothalamic dysfunction which had not been present prior to operation. Seventeen experienced recurrence of symptoms in the first 6 months after operation. In most of these the symptoms of intracranial hypertension returned, with much loss in vision as evidence of refilling of the cystic

tumor. In 18 patients symptoms of a recurrence appeared from 1 year to 10 years after operation. The average remission of symptoms lasted for more than 2 years in this group.

At intervals varying from 2 months to 10½ years, operations for recurrence were carried out 11 times among 11 patients in the series. Three postoperative deaths occurred after the secondary operation for recurrence.

Because it is generally felt that roentgen-ray irradiation has little or no effect on these tumors, it might be well to give a few of the details concerning 10 patients who were benefited by irradiation. One patient who had received roentgen irradiation prior to operation was completely relieved of symptoms for a period of 3 years. A recurrence of symptoms at the end of that time was not checked by irradiation, and operation revealed a cystic adamantinoma.

Another patient who received preoperative irradiation experienced a remission of symptoms for a period of 2 months, but operation was resorted to after a second course of irradiation had failed to bring about improvement.

A patient who had received a series of radium treatments followed by roentgen therapy was relatively free of symptoms for a year. Another course of roentgen radiation relieved the recurrent symptoms for 4 years, at the end of which he was operated upon because of bitemporal defects in the visual fields. A course of radiation was given postoperatively, and more than a year later (at the time of this report) he was in good health and had normal visual fields and ocular fundi.

Three patients received roentgen therapy after their second operation for recurrence. Two of them remained in good health for a year, at the end of which a second course of irradiation was given because of a recurrence of symptoms. One of these patients was free of symptoms 8 years after the last treatment; the other lived for more than 2 years after the final course of irradiation. The third patient was free of symptoms for 7 months after operation. He then received irradiation because of visual loss; a second course was given 2 months later. At the time of this report, remission of symptoms has persisted more than a year.

Three patients who had a recurrence of symptoms 2 months, 4 months, and more than 4 years, respectively, after operation were relieved of symptoms by roentgen irradiation. The first patient required a second course of irradiation, and was in fairly good health more than 7 years later. The second patient was well, except for mild hypopituitarism, a year later. The third patient was still free of symptoms more than 3 years later. The final patient of this group received roentgen therapy postoperatively, and a second course about 2 months later. Except for slight ataxia, she had been free of symptoms for more than 8 years at the time of this report.

A presentation of end results obtained in a series of pituitary adamantinomas spread over a period of 32 years, many of the lesions associated with recurrences that are potential if not actually proved by secondary operations, offers unusual difficulties. Of the 96 patients who underwent surgical operation, 38 died in the hospital, giving a hospital mortality rate of 40 per cent. Of the 58 patients who survived the operative procedure, 14 were operated on in 1944 or more recently. Of the remaining 44 patients, 3 are untraced or had not been followed for 5 years. Of the 41 traced patients, 21 or 51 per cent, lived 5 or more years after leaving the hospital. Five of these patients survived 10 years or longer. Two were living 13 years after surgical operation and 1 was living 20 years after operation. At the time of this study, 17 patients were known to be living a year or more after operation; of this group 13 were carrying on some type of useful activity.

SUMMARY

A review of the embryologic aspects of the pituitary gland and a histopathologic study of 100 cases of so called craniopharyngioma demonstrates that the name "pituitary adamantinoma" is the most logical one to designate this tumor. In reviewing the 100 cases, it was found that this tumor occurred most commonly in the second decade of life, but that 47 per cent of the patients were more than 20 years old. Headache and loss of vision were by far the most common symptoms, followed by endocrine disturbances, drowsiness

and signs of involvement of other neighboring structures. Roentgenologically, calcification of the tumor was observed in only 56 per cent of cases. Ten patients experienced remission or abatement of symptoms that can be attributed definitely to roentgen-ray irradiation. The surgical treatment of these tumors is discussed briefly, and the end results obtained for the 96 patients who were operated on at the Mayo Clinic are given.

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PRIMARY TUMORS OF THE CRANIAL BONES

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COMPARATIVELY little attention has been directed to the subject of primary neoplasms arising in the bones of the cranium. This may be due to the relative rarity of such lesions; their low incidence is seen in the figures of Geschickter, who, in a series of 500 bone neoplasms reported in 1936, found only 13 or slightly more than 2 per cent arising in the calvarium.

At Memorial Hospital between 1926 and 1948 we observed 888 primary malignant neoplasms of all bones, of which only 7 (0.8 per cent) had originated in the bones of the cranium. During the same period a study of another group of 630 benign tumors of bone showed only 15 (2.4 per cent) to be of cranial origin. This latter figure is perhaps too low owing to the fact that all records of benign cases which lack pathologic confirmation are destroyed after a 10 year interval.

The bones of the cranial vault, being ossified directly from primitive connective tissue, are not likely to develop primary tumors, while most other bones, including those of the cranial base, develop from connective tissue through a complex intermediary process of cartilage degeneration and absorption. Most primary bone tumors arise as a result of the transition incident to the development of cartilaginous or endochondral bone.

Historical. Those interested in the historical aspect of cranial neoplasms are referred to Moodie's (13, 14) studies of the paleopathology of Egyptian and Peruvian mummies as well as a collection of skulls of pre-Columbian Peruvian Indians. These include a few benign tumors and an apparent osteogenic sarcoma of the cranial vault of an adult probably antedating 1532.

Memorial Hospital series. This comprises 15 benign and 7 malignant tumors primary in the cranial bones. It is likely that a considerable number of benign cases, because of their frequent freedom from symptoms and relatively stationary size, never reach a clinic, for we should expect a higher incidence of osteomas. The benign group includes 7 osteomas, 6 hemangiomas, 1 giant cell tumor, and 1 intracranial hyperostosis. Other benign tumors likely to occur in the cranium and not represented in this series are cholesteatomas and osteochondromas.

The group of 7 malignant tumors includes 4 osteogenic sarcomas, 1 spindle cell sarcoma, and 2 solitary plasma cell myelomas or plasmacytomas. Of the 4 osteogenic sarcomas, 1 arose in Paget's disease, and 1 was superimposed on myositis ossificans. In addition to the types of primary malignant tumors in this series, Ewing's tumor, chordoma, and fibrosarcoma may be encountered. (Table I.)

BENIGN TUMORS

Of the cranial bones involved by a benign tumor the frontal was the most often affected (5 instances) while in no case was the occiput implicated. As to sex, females predominated 10 to 5. The youngest patient was a female of 11, and the oldest a female of 59. The majority were over 30 years and the average age was 36 years. Save for the presence of a tumor there were no symptoms in 10 or 67 per cent of the cases; 2 patients complained of head-

TABLE I.—CLASSIFICATION OF TUMORS OF CRANIAL BONES

(Memorial Hospital series of 22 cases)

Benign	No. cases
Osteoma	7
Hemangioma	6
Intracranial hyperostosis	1
Giant cell tumor	1
Total	15
Malignant	
Osteogenic sarcoma	3
Osteogenic sarcoma arising in Paget's disease	1
Spindle cell sarcoma	1
Plasma cell myeloma, solitary	2
Total	7

From the Bone Tumor Department, Memorial Hospital, New York.

TABLE II.—PRIMARY BENIGN OSSEOUS CRANIAL TUMORS (Memorial Hospital Series)

No.	Name	Site of lesion	Trauma	Age years	Sex	Presenting symptom	Size of tumor cm.	Roentgen diagnosis	Treatment	Pathologic diagnosis	Follow-up and remarks*
1	L.G.	L. temporal	o	59	F	Lump	4	Benign osseous	None	—	2 yrs. Clinically an osteoma
2	B.Z.	R. temporo-parietal	o	27	F	Headache	4×4×1	Osteoma	Excision elsewhere	—	None
3	A.T.	R. frontal	+	40	F	Painful lump (8 yrs.)	3.5×3.5×1 o	Osteoma	Radium elsewhere; none here	—	5 years; no change
4	L.Z.	L. occipito-parietal	o	40	F	Lump	2.5	Osteoma	None	—	3 years; no change
5	W.C.	L. parieto-occipital	+	16	M	Lump	3 o	Spongy osteoma	None	—	None
6	P.M.	L. frontal	?	11	F	Lump	1.5	Osteoma	Excision	Necrotic bone	9 months, NED
7	R.M.	R. frontal	o	21	M	Lump	1.5	Benign tumor	Excision	Osteoma	1 yr. 3 mo., NED
8	L.G.	L. frontal	o	32	F	Painful lump	1.0	Hemangioma	Excision	Angioma	4 months, NED
9	N.B.	L. frontal	o	45	M	Lump	2×2×0 5	Angioma	Excision	Hemangioma	6 months, NED
10	V.D.	L. frontal	o	44	F	Lump	3.5	Demarcated area of destruction	Excision	Hemangioma	6 months, NED
11	C.W.	L. frontal	o	55	M	Lump	2	Benign	Excision	Angioma	2 years, NED
12	A.G.	L. frontal	+	38	F	Lump	2.5	Meningioma	Excision	Angioma	2 years, NED
13	A.F.	L. frontal	o	34	F	Enlarging lump	2.0	Spongy osteoma	Excision	Hemangioma	9 months, NED
14	R.B.	Fronto-parietal	?	46	F	Headache	—	Hyperostosis frontalis interna	None	—	None
15	W.M.	L. temporal and zygoma	o	39	M	Impaired hearing	—	Irregular area of bone destruction	Irradiation	Aneurysmal chondromatous giant cell tumor	8½ yrs. No evidence of recurrence

*NED—no evidence of disease

ache, 2 of a painful swelling, and 1 of impaired hearing. For a summary of the cases of benign tumor see Table II.

Osteoma. This type of tumor usually appears before the age of 30, and its most frequent site is the frontal bone. It usually appears as an eburnated or ivorylike tumor arising from either the outer or the inner table of the skull, the former being more common. It frequently is found near suture lines in the parasagittal region. It varies considerably in size, the smaller tumors tending to be hard in consistency and the larger ones spongy. The roentgenographic appearance of the hard type is characteristic, showing a rounded area of homogeneous increase in density arising usually from the outer table, while the spongy variety is composed of cancellous bone, the surface of which may be thick or thin and in the latter easily broken. Tangential exposures usually reveal a smooth, domelike surface which is continuous with the outer table of the calvarium. The density varies considerably with the type of tumor. The high incidence of eburnated osteomas in the frontal and facial regions is apparently due to periosteal or subperiosteal proliferation as normal bone growth in regions where such growth persists.

CASE 1. L. G., a 59 year old Hebrew female, was first seen in October, 1942, with a history of a painless, enlarging nodule of the left temporal region for 4 years. Examination revealed a bony, fixed, 4 centimeter, smooth mass. Admission roentgenograms disclosed a dense clear-cut shadow of increased bone density (Figs. 1 and 2). No treatment was given. Subsequent examinations over a 2½ year period showed no change. Diagnosis was osteoma, left temporal region.

CASE 2. B. Z., a 57 year old Hebrew female, was first seen in November, 1943, with a history of a mass in the right parietal region for 7 years. Examination showed a smooth, bony, 4 centimeter mass elevated for 2 centimeters. Roentgenograms revealed the presence of a benign bony density. The tumor was removed elsewhere in January, 1944. No follow-up Diagnosis was osteoma, right parietal region.

Fig. 1. Case 1. Osteoma of the left temporal area.

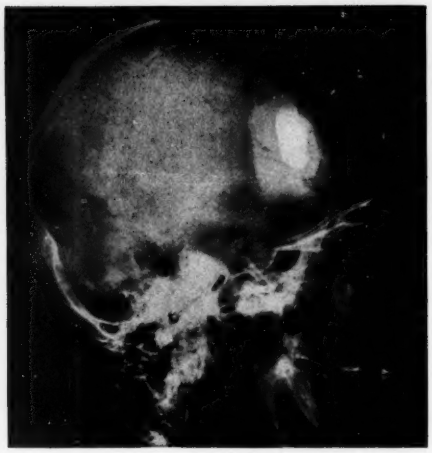

Fig. 2. Lateral view of same patient.

CASE 3. A. T., a 40 year old white female, was first seen in August, 1940, with a history of trauma to the right frontal region 8 years previously, and again at the same site 8 months later. A hard, local swelling had persisted since the initial injury without symptoms until 6 weeks prior to her first visit when she developed rightsided headaches and frequent spots before her eyes. She had received two radium treatments elsewhere without change in symptoms or tumor. Examination disclosed a smooth, bony, 3.5 centimeter, elevated mass located in the right upper frontal region. Roentgenograms showed a rounded, bony density. No treatment was given. The patient was observed for 5 years without change. Diagnosis was osteoma, right frontal region.

CASE 4. L. Z., a 40 year old Hebrew female, was first seen in December, 1939, with a history of a small, asymptomatic, left postauricular swelling for 15 years. Physical examination disclosed a 2½ centimeter smooth, elevated, bony mass in the left occipitoparietal area. Roentgenograms revealed an osteoma in the described area (Fig. 3). Patient was observed for 4 years without evident change. Diagnosis was osteoma, left occipitoparietal area.

CASE 5. W. C., a 16 year old white male, was first seen in April, 1945, with a history of a painless swelling on the top of his head which had been present since a fall at the age of 1 year. There were no symptoms until 3 weeks prior to admission when he developed a severe headache which lasted for 3 days. Examination showed a smooth, bony, 3 centimeter prominence in the parieto-occipital region just to the left of the midline. Tangential roentgenograms revealed an ovoid area of decreased density with clear-cut margins and with expansion of the outer table, the appearance suggesting a spongy osteoma. The patient failed to return for follow-up. Diagnosis was osteoma, left parieto-occipital region.

CASE 6. P. M., an 11 year old white female, was first seen in December, 1940, with a history of a slowly growing mass in the left frontal region of 2 years' duration. Examination revealed a 1.5 centimeter bony prominence, lying beneath a cavernous hemangioma in the left frontal region. The latter had been treated with sodium morrhuate injections. Roentgenograms disclosed a small osteoma arising from the outer cranial table, elevated 0.5 centimeter. The tumor was excised in December, 1940. The patient made an uneventful recovery but failed to return for subsequent observation. Diagnosis was osteoma, left frontal region.

CASE 7. R. M., a 21 year old white male, was first seen in September, 1947, with a 4-year history of a painless lump of the right frontotemporal region which was removed elsewhere 3 years before and had recurred 2 years later, after which it had increased in size. Examination disclosed a 1.5 centimeter bony, smooth swelling, not attached to skin. Excision was done in September, 1947. Pathologic diagnosis was osteoma. No recurrence was noted in 15 months. Diagnosis was osteoma, right frontotemporal region.

The sites of tumors in this small group of 7 cases were evenly distributed over the vault of the skull. Antecedent trauma was a factor in 1 case, and probably in another. The tumor appeared at ages ranging from 1 to 55 years, the average being 23 years. There were 5 females and 2 males. In 3 of the 7 cases the lesions were excised. Two of the remaining 4 patients were followed in the outpatient department after the roentgen diagnosis had been established.

No treatment may be required for symptomless osteomas which are not increasing in size. Surgical removal should be reserved for those whose course is associated with pain or headache or rapid enlargement.

Hemangioma. The literature of cranial hemangiomas has been reviewed by Wyke and Rowbotham, the former collecting 61 cases reported during the past 100 years, of which 40 fit the criteria of proved solitary cranial lesions. The findings of these authors indicate the rarity of the tumors, constituting 0.2 per cent of osseous neoplasms, yet because of the infrequency of cranial osseous neoplasms, constituting 10 per cent of primary benign neoplasms of the skull. They further observe that these tumors are most frequent in the fourth decade, occur two to three times as frequently in females as in males, and most often involve the parietal and frontal bones in that order. Hemangiomas are usually cavernous, consisting of large blood spaces embedded in connective tissue of variable cellularity and lined by elongated flattened cells. The elastic tissue and muscle of normal vessel walls are absent. The characteristic honeycombed roentgen appearance is due to remodeling caused by bone destruction and formation; in addition one sees clearly defined margins, and frequently trabeculae radiating from the center of the tumor producing the classical "sunburst" appearance.

In the following 6 cases the diagnosis was confirmed by examination of tissue following excision of the tumor:

CASE 8. L. G., a 32 year old white female, was first seen in December, 1940. She had noticed a hard growth in the frontal region for 1 year, and for 6 months had experienced throbbing local pains and headaches. Examination revealed a 2 centimeter hard, fixed, spherical tumor in the left frontal region. A roentgen diagnosis of osteoma was made based on findings of a well demarcated area of bone loss with spicules radiating from the center. The tumor, which was excised in August, 1942, proved to be a firm, circumscribed mass, and on microscopic examination was pronounced an angioma. Diagnosis was angioma, left frontal bone.

CASE 9. N. B., a 45 year old white male, was first seen in April, 1942. One year previously he had noted a small, painless lump in the forehead which had steadily increased in size. Examination revealed a bony, fixed, 2 centimeter mass in the left medial supraorbital region. The roentgen appearance was

Fig. 3. Case 4. Osteoma of left occipitoparietal area, showing characteristic rounded area of homogeneous density.

compatible with hemangioma, showing a 2.5 centimeter circular area of bone loss involving the outer table and diploic regions adjacent to the left frontal sinus (Fig. 4). Operation on April 13, 1942 disclosed a bluish, 2 centimeter elevated tumor with a bony wall. It contained spongy, friable, bony tissue which was removed, and the cavity was swabbed with zinc chloride solution. A pathologic diagnosis of hemangioma was rendered. After 2 months the patient failed to return for examination. Diagnosis was hemangioma, frontal bone.

CASE 10. V. D., a 44 year old white female, was first seen in November, 1941, with a painless, frontal lump of 2 years' duration. Examination revealed a small, hard, fixed mass in the left frontal region. Skull roentgenograms disclosed a 3.5 centimeter, well marginated area of radiolucency with some reticulations in the described area. The appearance was suggestive of cholesteatoma, angioma, or osteochondroma. The tumor was excised (November 6, 1941) and on microscopic examination was pronounced hemangioma. Six months later the patient had a radical mastectomy performed elsewhere for a carcinoma of the breast, which diagnosis was confirmed by Memorial Hospital laboratory. She was then lost to follow-up. Diagnosis was hemangioma, frontal bone.

CASE 11. C. W., a 55 year old white male, was first seen in May, 1946, with a painless swelling of the left frontal region for 4 years. There was no history of trauma. Examination revealed a 2 centimeter, smooth, elevated, bony lesion which was tender to palpation. Skull roentgenograms disclosed an area of radiolucency in the frontal bone. Blood calcium, phosphorus and phosphatase levels were normal. The tumor was excised on June 5, 1946. Pathologic diagnosis: "suggests angioma

Fig. 4. Case 9. Hemangioma of frontal bone shown in tangential view. "Sunburst" appearance of radiating trabeculae is evident.

rather than osteoma; may be hyperostotic." After 2 years there was no evidence of disease. Diagnosis was angioma, left frontal bone.

CASE 12. A. G., a 38 year old white female, was first seen in March, 1944, with a history of a painless swelling of the right frontal region which appeared a few months after she had bumped her forehead. Following a short initial period of growth it remained unchanged in size. Examination disclosed a well defined bony mass not attached to overlying skin. Skull roentgenograms revealed a circular area of decreased density in the right lateral frontal bone, consistent with a diagnosis of meningioma. On March 15, 1944, the lesion was excised. Grossly the tumor consisted of rather spongy bone, slightly dome-shaped, measuring 2.5 by 0.8 centimeters, covered by a thin shell of cortical bone; the tumor extended to the dura. Pathologic diagnosis was angioma of bone. The patient was free of evidence of recurrence for 2 years, after which she could not be traced. Diagnosis was angioma, right frontal bone.

CASE 13. A. F., a 34 year old white female, was first seen in July, 1947, with a history of an enlarging, painless lump of the left forehead for 1 year. Examination revealed a 2 centimeter slightly elevated, bony, nontender swelling. Roentgenograms suggested spongy osteoma. The patient preferred observation, but in 1 year the tumor had increased to 3 centimeters and was then (September 22, 1948) removed. Pathologic diagnosis: hemangioma. Examination 9 months later revealed no evidence of disease. Diagnosis was hemangioma, left frontal bone.

In this group of 6 hemangiomas the incidence of females to males was 2 to 1. All tumors were located in the frontal bone. Trauma was noted in 1 case. The average age was 42 years. Only 1 tumor was painful. The average size was 2 centimeters in diameter. Roentgen diagnosis was made in 2 cases. All were treated by excision. None has shown evidence of recurrence since operation.

Hyperostosis frontalis interna. This condition is most frequently noted in adolescence. It usually involves the inner tables of the parietal and frontal bones near the coronal suture.

CASE 14. A 46 year old white female was first seen in December, 1943, with a chief complaint of severe headaches which had been present since she sustained an injury to the frontal bone in 1941. She had also noted thirst and water retention following the accident. Physical examination was negative. Skull roentgenograms revealed considerable irregularity in density of the frontal and anterior regions of both parietal bones with calcification in the falx cerebri. She was admitted for studies in December, 1943, and July, 1944. No significant findings were obtained. She was not followed after 15 months.

It seems likely that the patient's cranial symptoms were posttraumatic rather than due to the hyperostosis which was probably present for a considerable time before the injury.

Giant cell tumor. Giant cell tumors are usually confined to intracartilaginous bones with the exception of the giant cell epulis which develop around the roots of deciduous teeth. In the skull their development from chondrocranium is shown by Pancoast, Pendergrass, and Shaeffer's review of 6 cases in the literature. Only 1 of these developed in membranous bone in the frontal region; 2 arose from the sphenoid bone, one from the mastoid region, and 2 from the occipital region. According to these authors, the consensus is that the etiology of these tumors rests with trauma and associated hemorrhage causing reactive changes. Roentgenographically these tumors demonstrate a well demarcated area of bone rarefaction. They have a tendency to recur locally; this took place in 3 of the 4 cranial tumors in Geschickter's series, but none of his patients died of the disease.

CASE 15. W. M., a white male of 39 years, was first seen in October, 1939. His chief complaint was

TABLE III.—PRIMARY MALIGNANT OSSEOUS CRANIAL TUMORS (Memorial Hospital Series)

No.	Name	Site of lesion	Trauma	Age years	Sex	Presenting symptom	Interval between onset and treatment months	Nature of tumor	Pathologic diagnosis	Results	Remarks
16	B.H.	L. parieto-occipital	o	21	F	Painless lump	14	Soft	Osteogenic sarcoma	Died from disease	Survived 9 mo.
17	G.Z.	L. temporal	+	18	M	Headache	1	Bony	Osteogenic sarcoma in myositis ossificans	Died from disease	Survived 7 mo. Widespread visceral metastases
18	C.R.	L. orbit	o	22	F	Pain in left eye	1	Soft	Osteogenic sarcoma	Died from disease	Survived 2 mo.
19	I.B.	Midfrontal	o	74	M	Swelling	6 wk.	Soft	Osteogenic sarcoma in Paget's disease	Died from cerebral vascular accident	Survived 2 mo. Marked regression
20	W.B.	Midparieto-occipital	+	28	M	Headache	3.5	Spongy	Spindle cell sarcoma	Died from disease	Survived 8 mo.
21	M.K.	Midfrontal	o	72	M	Lump	3.5	Soft	Plasma cell myeloma	Living without disease	Followed 6 yr.
22	C.F.	Parietal	+	54	M	Lump	12	Soft	Plasma cell myeloma	Living without disease	Followed 15 mo.

increasing deafness for 10 months. One week prior to admission an excision biopsy of the zygoma had been taken elsewhere. Histologic diagnosis was aneurysmal giant cell tumor. Physical examination revealed a granulating scar above the left ear. A small, firm, pedunculated growth in the left auricular canal presented from the roof. Biopsy showed this to be an aneurysmal chondromatous giant cell tumor of borderline malignancy. High voltage therapy, 6,400 roentgens, was given to the left temporomandibular joint region over a 5 week period beginning in November; this was followed by considerable pain. Examination disclosed nothing significant except diminished hearing in the left ear until radionecrosis of the left ear developed and in May, 1940, five months after completion of therapy, the ear was excised. The operative area healed slowly. In March, 1944, he had attacks of labyrinthine dizziness. He has worn a plastic ear since 1941. Subsequent roentgenograms have shown a persisting area of destruction in the temporal bone above and anterior to the left mastoid process. Except for sensitivity of the left side of the head he is well, without evidence of recurrence of the disease, 8½ years later.

This case represents a type of giant cell tumor which from microscopic appearance had malignant proclivities but which was successfully treated by radiation. However, necrosis of the aural cartilage necessitated amputation of the ear. Diagnosis was aneurysmal chondromatous giant cell tumor.

Differential diagnosis. The roentgen characteristics are of most importance in the differential diagnosis of benign cranial tumor. The typical roentgen appearance of osteomas is a dense, rounded, homogeneous shadow protruding from the outer or infrequently from the inner cranial table. Spongy or cancellous osteomas arising in the diploe are uncommon; they usually attain a larger size. Hyperostoses due to meningioma show more definitely radiating spicules extending at right angles to the vault. Hyperostosis cranii is usually bilateral and frontal in location. Osteoid osteoma, described by Jaffe in 1935, has not been reported in the skull.

Hemangiomas, as described by Camp, are characterized by honeycomb architecture with widening of the intertrabecular spaces and increased density of the trabeculae. They must be differentiated from cholesteatomas (epidermoidomas) which exhibit an area of rarefaction with well defined margins of increased density, are located in diploic spaces and grow slowly (3), and meningiomas which have vertical rather than radial striations and do not show reactive sclerosis (22). Osteochondromas of the base of the skull are rare. King and Butcher in 1944 reported 9 cases, including 1 of their own, which on roentgenograms showed areas of increased density scattered throughout the tumor.

MALIGNANT TUMORS

Of the malignant cranial osseous tumors, osteogenic sarcoma is the type most frequently encountered. The part played by trauma in its etiology has aroused considerable conjec-

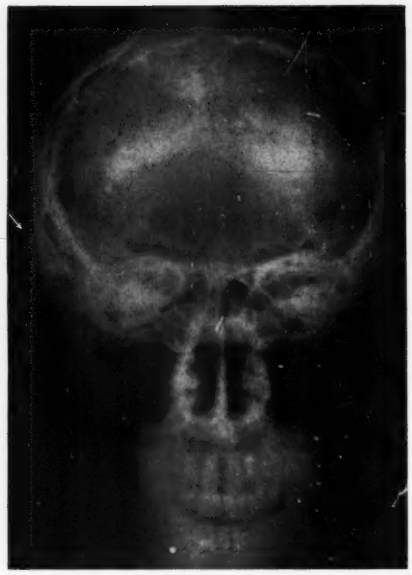

Fig. 5. Case 17. Osteogenic sarcoma of the temporal region arising in myositis ossificans, showing partly calcified mass protruding outside cranial vault.

ture (2, 18). Shaw postulated that extravasated blood following injury acts as a chronic irritant and stimulus to physiologically unnecessary proliferation, with consequent absence or insufficiency of factors to induce differentiation. However, there is widespread skepticism among pathologists as to the role played by trauma in the origin of sarcoma. In the present series, antecedent trauma was considered a possible factor in 3 of the 7 cases, 2 of which were sarcoma and 1 plasmacytoma (Table III, Cases 17, 20, 22). In Case 17 of this group, the diagnosis of osteogenic sarcoma in myositis ossificians was made after a review of the sections, tending to strengthen the likelihood of trauma in its etiology. Osteogenic sarcomas are rapidly growing, locally destructive, and metastasize early. In our 5 cases, 3 patients died from local extension while only 1 from distant metastases; and in 1 case which developed in the presence of Paget's disease the patient apparently did not die from sarcoma. Kirshbaum in a review of the literature of sarcoma in Paget's disease, in 1943, found osteogenic sarcoma of the skull in 8 of a group of 208 cases of Paget's disease, or in 3.8 per cent. In the same group 22 cases of osteogenic sarcoma of other bones developed, an incidence of 14.4 per cent. Pack and Braund who also reviewed the literature, reported 7 cases, including 2 from their experience, in which osteogenic sarcoma developed in myositis ossificans. Fibrosarcomas, not represented in this series, arise from the outer portion of the periosteum and eventually invade and destroy bone. Chordomas of the cranial region originate from embryonic notocord remnants arising in the spheno-occipital junction. Virchow first described the tumor in 1856. They occur between the third and fifth decades and are likely to result from trauma with rupture of the enveloping cartilage. The literature of these tumors has been well reviewed (1, 7, 8). Ewing's endothelioma is encountered most frequently in the bones of the extremities, especially the femur and tibia; its occurrence in the cranium is rare.

Following are reports of 5 cases of sarcoma:

CASE 16. B. H., a 21 year old white female, was admitted to Memorial Hospital in August, 1943, with the following history: she first noticed a lump in the left occipitoparietal region 14 months before, which had grown slowly. Four months prior to admission she first noted local pain. Examination revealed a hard, nodular, 7 centimeter mass, elevated 1.5 centimeters, located in the left occipitoparietal region, fixed to the skull with several soft areas present. Enlarged, firmly fixed lymph nodes were present in the left posterior cervical triangle and the postauricular region. Roentgenograms showed a large area of increased density with destruction of the outer table and a marked thickening with irregular bony tumor having radiating spicules. Diffuse calcification was present throughout the tumor. The tumor suggested osteogenic sarcoma, which diagnosis was confirmed by biopsy of the cranial lesion and a cervical node. The lesion was deemed too advanced for effective therapy so the patient was discharged without treatment. She died in May, 1944, nine months after admission or 23 months after the tumor was first noted. Final diagnosis was osteogenic sarcoma of left occipitoparietal region with metastases to lymph nodes of the left cervical region.

CASE 17. G. Z., an 18 year old white male, was admitted in March, 1934, with the following history. Three months previously he was struck a moderate blow on the left temporal region while playing basketball; 1 month later a swelling was noted at the site of the injury. In the following month he experienced left-sided headaches. He had lost 15 pounds in weight. A biopsy was taken at another hospital 1 month after the injury, following which the patient

Fig. 6. Case 19. Osteogenic sarcoma originating in Paget's disease of the skull.

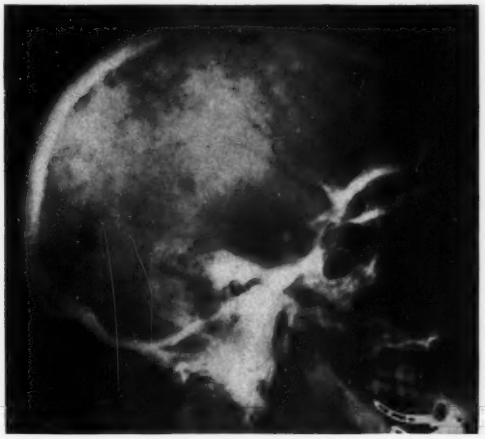

Fig. 7. Lateral view of the same patient as shown in Figure 6.

received 4 x-ray treatments. A progressive swelling of the left temporal region had been noted for 2 months prior to admission. His general health was good. Examination disclosed a slight protrusion of the mandible, and diminished hearing in the left ear. His hands were enlarged suggestive of early acromegaly. There was a broad, smooth, elevated, diffuse swelling in the left temporal region adherent to the skull. It measured 12 by 12 centimeters, was elevated 4 centimeters, and was of uniform bony hardness except over the most prominent portion where there was a slight depression beneath a healed incised wound. Roentgenograms of the skull disclosed a partly calcified mass protruding from the left temporal region (Fig. 5). There was no evidence of pulmonary metastases. The findings were consistent with the diagnosis of osteogenic sarcoma. A diagnosis of myositis ossificans had been made prior to the patient's admission. A biopsy was done on April 4, 1934, revealing a gray, firm, but not bony, 1 centimeter tumor in the soft tissue extraneous to bone. A pathologic diagnosis of osteogenic sarcoma was made. A later review of sections substantiated the diagnosis of osteogenic sarcoma arising upon myositis ossificans.

Radium pack therapy was given in daily doses of 8,000 milligram hours, for a total of 76,000 milligram hours to the left temporal region, administered between April 9 and April 17, 1934. In addition he received Coley's toxins. At the conclusion of treatment the patient was discharged with no discernible change. He gradually became worse and in August developed left upper abdominal and back pain. He died on August 30, 1934, surviving 7 months. A partial autopsy revealed a consolidated and collapsed left lung with extension of the disease to the left diaphragm, ribs, left kidney and splenic flexure. Submitted sections of the diaphragm and kidney showed metastases of osteogenic sarcoma. Diagnosis was osteogenic sarcoma of the cranium with extensive thoracic and abdominal metastases.

CASE 18. C. R., a 22 year old white female, was first seen on July 25, 1929. Six weeks before she had noted onset of severe pain in the left eye and left-sided headaches with gradually developing disturbed vision in the left eye. She had been hospitalized elsewhere and a diagnosis of spindle cell osteogenic sarcoma had been made on biopsy material obtained from the sphenoid and ethmoid sinuses. Examination on admission showed the left nasal cavity blocked by an edematous mass which extended to within 2 centimeters of the anterior naris. There was moderate left exophthalmos with impaired extraocular movements, prominence and tenderness of the left malar eminence, and absent reaction to light and accommodation in the left eye. The diagnosis of osteogenic sarcoma was verified microscopically. Roentgenograms disclosed a 4 centimeter area of bone destruction in the medial portion of the left orbit. Rapid destruction was noted on comparing admission films with those taken 1 month previously. While surgery was considered the treatment of choice, the patient's condition was deteriorating too rapidly to attempt it. She was discharged 3 weeks after admission, and died 2 weeks later, 3 months after the onset of symptoms. Final diagnosis was osteogenic sarcoma of left orbit.

CASE 19. I. B., a 74 year old Hebrew male, was first seen on May 24, 1948, with a history of increasing pain and numbness in the right hip and leg for a period of 8 months, and a painless swelling in the frontal and left parietal region for the past 6 weeks. He had been treated elsewhere 6 weeks prior to admission where a biopsy of the frontal region had dis-

closed osteogenic sarcoma. High voltage roentgen therapy had been given to the frontal and parietal regions through two portals, using 350 roentgens, alternating daily for a total of 2,450 roentgens to each portal; in addition the lumbar vertebrae received 1600 roentgens of high voltage palliative roentgen therapy. Examination on admission revealed a 3.5 centimeter swelling in the midfrontal region, elevated ¾ centimeter, which was partly soft and suggested necrosis; several small satellite swellings were present. In the left parasagittal parietal region was a 1 centimeter swelling. These areas corresponded to areas of radiolucency in skull roentgenograms, which showed widespread Paget's disease of the skull, pelvis, and lumbar vertebrae, with radiolucent areas in the frontal and parietal regions suggesting possible sarcomatous degeneration (Figs. 6 and 7). By the end of June, 2 months after treatment, there was marked regression of the tumor of the frontal region. On July 3, 1948, he developed progressive paralysis of the left arm, and a few days later marked difficulty in swallowing and in articulation. He became comatose and died several days later, apparently of a cerebral vascular accident. Final diagnosis was osteogenic sarcoma of frontal bone developing in Paget's disease.

CASE 20. W. B., a 28 year old white male, who, 3 months prior to admission on October 20, 1925, had been struck on the occiput by a falling packing case. Considerable increasing local swelling followed. Frequent headaches supervened. On October 4 he was admitted elsewhere where a biopsy of the occipital bone revealed osteogenic sarcoma. On admission to Memorial Hospital, 3 weeks later, the biopsy wound was still open and packed with gauze; otherwise the examination was essentially negative. Roentgenograms revealed a 5 centimeter irregular area of bone destruction in the parieto-occipital region centering in the midline and involving both cranial tables. Radium therapy instituted on admission was given at intervals until July, 1927; this was supplemented by Coley's toxins. The patient remained symptom-free without evidence of disease until December, 1930, or 5 years after onset, when he complained of occipital pain. Examination showed a slight elevation at the site of the original tumor. Further radium therapy followed by Coley's toxins was given, resulting in a disappearance of pain so that the patient was able to return to work. The pain recurred in July, 1931, and he was given further radium therapy; this was repeated in November, 1932 for multiple areas of local softening which had developed. There was temporary amelioration of pain. In June, 1933 a division of the occipital nerves was done for pain; the operative wounds did not heal and fungating tumors appeared in both. At operation an 8 centimeter area of necrosis in the midoccipital region was noted. The tumors grew rapidly, the patient developed right paraplegia on September 11, 1933, and died on September 18, 1933.

It seems probable that a recurrence developed in 1931, six years after the first appearance of the tumor, which was briefly controlled by treatment, although the headaches persisted. Section of the occipital nerves relieved the pain somewhat but was followed by rapid local tumor growth. The significant fact is that the tumor was kept under control for 8 years. Final diagnosis was spindle cell type of osteogenic sarcoma of occipital bone with intracranial metastases and right paraplegia.

The foregoing group of 5 cases, all primary sarcomas arising in bone, included 4 osteogenic sarcomas and 1 spindle cell sarcoma. In 4 cases the tumor was located in the vault, and in 1 in the orbit. The case of spindle cell sarcoma is notable because patient survived for a period of 8 years; this case was reviewed by the Committee of the Bone Sarcoma Registry, American College of Surgeons, and while there was a divergence of opinion so that an unequivocal diagnosis of osteogenic sarcoma is lacking, from the clinical and roentgenographic standpoint the case was regarded as unquestionably one of primary bone sarcoma. Excluding the case which developed in the presence of Paget's disease in a 72 year old male the ages ranged from 18 to 28, the average being 22 years, bearing out its occurrence in adolescence or early adult life. Antecedent trauma occurred in 2 cases. Excluding the patient with spindle cell sarcoma who survived 8 years, the average survival was 5 months. It is worthy of note that 4 of the 5 tumors were soft. Symptoms of pain or headache were present in 3 of the 5 cases. One case of osteogenic sarcoma developed in myositis ossificans and survived for 7 months.

Plasma cell myeloma. Most plasma cell myelomas are multiple but occasionally solitary lesions are encountered which run a protracted course and respond well to irradiation therapy or excision. Stewart and Taylor in reporting 4 cases in 1932 observed that solitary plasmacytomas or plasma cell myelomas show no Bence Jones proteinuria and relatively few mitoses with no extreme variation of plasma cells. They warned against mistaking them for endosteal tumors of high malignancy. Willis in 1941 proposed two criteria for diagnosis, i.e. (1) no other lesion followed the appearance of the initial lesion for 1 year, and (2) no Bence Jones protein was found for 1 year. Esposito, in a review of the literature in 1941, found only 1 verified case of solitary myeloma

of the skull, viz., the case reported by Mathias in 1935, a 65 year old male with a frontal bone lesion who showed negative skeletal roentgenograms and Bence Jones protein after 18 months. His own case, a 69 year old male with a tumor of the frontal bone had been followed 5 months at the time of his report. In our 2 cases, one, a 72 year old male was followed for 6 years after receiving roentgen therapy, at which time a skeletal survey was negative for lesions other than the arrested primary frontal lesion, and the other, a Brazilian physician, reported that no evidence of other tumor could be found 15 months after treatment.

Single myelomas occur in older individuals as do multiple myelomas which usually occur after 40. In 1 of our cases there was a history of antecedent trauma. Both patients responded favorably, one to roentgen therapy, the other to surgery followed by roentgen therapy.

CASE 21. M. K., a 72 year old white male, was first seen in January, 1942, four months after having noticed a lesion of the forehead which had steadily enlarged; there was occasional dizziness and a feeling of fullness in the head. Examination revealed a 5 centimeter cystic mass in the right midfrontal region with no underlying bone palpable. There was no skin attachment. Roentgenograms disclosed a 9 centimeter area of bone destruction in the midfrontal region, with well defined borders and some tendency to loculation. There was no reactive bone at the periphery. Destruction involved both tables. A skeletal survey was negative for other lesions. After a diagnosis of plasma cell myeloma was made from aspiration biopsy material taken on March 5, 1942, a course of deep roentgen therapy was given; 3,000 roentgens were administered using 300 roentgens on alternate days (factors: 250 kilovolts, 1.5 millimeters copper filter, 35 centimeters target skin distance, 9 centimeter cone). At the completion of treatment there was a 50 per cent regression in the soft tissue swelling. A second course of 2,400 roentgens was given 10 weeks after the first, employing the same method and factors, for a total of 5,400 roentgens. By August, 1942, seven months after first observation, complete regression of the frontal lesion had occurred, and there was roentgen evidence of partial bone regeneration. In April, 1948, six years after treatment, there was local, irregular recalcification of bone at the tumor site, the patient was asymptomatic, and a skeletal survey at that time was negative. Final diagnosis was plasma cell myeloma, solitary, of frontal bone.

CASE 22. C. F., a 54 year old male Brazilian physician, was first seen in June, 1947. One year previously he had first noticed a small swelling in the midposterior parietal region which he believed was the result of recent trauma. By May, 1947, it had attained a diameter of 3 centimeters. Roentgenograms disclosed an ill-defined area of decreased density in the posterior parietal region adjacent to the lambda, situated in the diploe. Biopsy taken elsewhere in May, 1947, was reported as showing a thick-walled, cystlike, dark, vascular area. At operation the cyst wall was removed and the bed electrocoagulated. Examination on admission, 1 month after the above treatment, showed a healed scar with no evidence of tumor. Submitted sections of the specimen were diagnosed as plasma cell myeloma. Blood calcium, acid and alkaline phosphatase, phosphorus, protein and urea nitrogen were normal. There was no Bence Jones proteinuria. High voltage roentgen therapy was given in daily doses of 300 roentgens for a total of 3,000 roentgens. After 15 months the patient reported no symptoms or evidence of recurrence. Final diagnosis was plasma cell myeloma, solitary, or parietal bone.

Observation of the clinical behavior of so-called solitary plasma cell myelomas reveals that these tumors exhibit low grade and only local malignant potentialities so that they are often considered of borderline malignancy.

Diagnosis. Osteogenic sarcoma shows destruction of bone usually with soft tissue swelling. In most cases osteoblastic activity is not sufficient to produce the appearance of bone in the expanding tumor. It must be differentiated from metastatic carcinoma. Occasionally lesions secondary to meningioma may produce a suggestive picture. Intracranial lesions cause a localized thinning of the internal table (4). Plasmacytoma must be differentiated from multiple myeloma by skeletal survey, bone marrow studies, and examination for Bence Jones proteinuria, and from cholesteatoma which exhibits a well demarcated area of decreased density with margins of increased density due to expansion of diploe.

SUMMARY AND CONCLUSIONS

This communication deals with a series of 22 neoplasms of the cranial bones of which 15 were benign and 7 malignant. Osteoma is the commonest of the benign tumors, and osteogenic sarcoma of the malignant ones.

Many of the benign neoplasms of the skull do not require treatment. Hemangioma may be dealt with surgically, and the same may be said for some of the osteomas.

Giant cell tumor of the cranial bones is very rare. It may be treated by roentgen therapy.

Sarcoma of the skull has an extremely unfavorable outlook since, owing to its location, it does not lend itself to radical surgery. With the technical advances in neurosurgery, and in view of the otherwise hopeless outlook, it is expected that more radical attempts to remove the primary site of the disease may be made in the future.

Myeloma of the skull is usually a manifestation of widespread disease. In the so-called "solitary" lesions, however, roentgen therapy may have value.

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COMPLICATIONS OF LATE PREGNANCY IN RABBITS INDUCED BY EXPERIMENTAL PLACENTAL TRAUMA

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THE present investigation was designed to evaluate, by animal experiment, a hypothesis concerning the biochemical mediation of certain acute complications of late pregnancy. The hypothesis is that a chemical mediator may enter the maternal circulation from the conceptus as the result of a process of "native extraction" and then cause characteristic pathology of late pregnancy.

In the present work, the pregnant rabbit proved to be a satisfactory experimental animal. Premature placental separations were produced artificially at laparotomy. Acute complications frequently followed; some of these have their counterparts among the complications of late human pregnancy.

So far as could be determined these complications depended upon fibrinogen coagulation, intravascularly. The most extreme reaction, shock with sudden death, depended upon a characteristic type of disseminated pulmonary thromboembolism.

In addition, in some animals, the coagulation reaction may have initiated a deficiency state, namely a defibrination of the circulating blood (1). However, such a deficiency would have gone unnoticed in the present study for no measurement was made to detect it, and no complications attributable to defibrination were observed. Instead, some if not all of the complications observed in the present limited study appeared to have been the result of the presence of fibrin, by coagulation from fibrinogen, not physiologically outside the vasculature, but pathologically within the vasculature.

METHOD

Placental trauma experiments. The abdomen of a rabbit of known gestation age was opened under conditions of surgical asepsis. This included soaping, shaving, washing the field of operation with alcohol, and finally draping with sterile towels; the operator's hands and arms were scrubbed with soap and rinsed in alcohol; the surgery was performed with bare hands.

The most frequent lesions resulting from the experimental placental trauma were in the liver. It was necessary to detect and exclude any animal with similar, pre-existing lesions by first inspecting the livers. Since the experimental lesions were visible grossly, this could be readily accomplished. In order to minimize the risk of producing lesions by mechanical trauma during this inspection itself, it was desirable to limit the inspection to visual observation only; therefore, the liver was not palpated or manipulated. With an extensive midline incision, the lower portions of the three larger lobes could be observed readily; these were the most frequent sites for the subsequent experimental liver necrosis, of which examples can be seen in Figures 1 and 3. No similar, spontaneous lesions were found in the areas inspected.

The experiment was then begun. Without tension on the mesometrium, a placental site was compressed between the thumb and index finger in such a manner as to tend to separate the placenta from the uterine wall.

It would have been of some interest to evaluate further the conclusion from the results recorded below, namely that placental trauma alone without actual placental separation would have been adequate to disperse tissue materials into the maternal circulation. However, this would require further experiments for in those which are recorded herein the manipulations were repeated until extensive or even complete placental separation was achieved.

Beginning with one uterus at a time, the placenta of the conceptus nearest the cervix was separated first, then the next, and the

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next, in order. Disturbance of the uterine circulation (4, 5) was minimal. As soon as one placenta had been separated, its portion of the uterus was allowed to fall back into the abdomen, in this manner proceeding to as many placental sites as were to be separated.

For these laparotomies, ether was used for anesthesia. To reduce the risk of confusing a possible accident of anesthesia with a pathologic response, the anesthetic was administered only until the beginning of the uterine manipulations; the ether cone was then removed, and the experimental procedure was carried out and the closure of the incision was accomplished quickly under the residual anesthesia.

Premedication with atropine reduced respiratory infections to a minimum. In one animal a pre-existing pulmonary abscess was found by gross inspection at sacrifice. This animal was excluded from the series.

The animals which were sacrificed as well as one with a promptly lethal reaction were at once subjected to post mortem examination. Thin slices of all tissues that were to be studied were fixed in formal alcohol within less than 20 minutes after death. The routine stain was hematoxylin and eosin. The animals were sacrified at appropriate intervals under ether anesthesia; this was administered deeply and rapidly to minimize agonal changes. The sacrifice was usually performed one day, after the placental trauma. A few animals were taken earlier or later to study the course of the lesions, particularly those in the liver.

Sensitivity of pregnant rabbits to placental extracts. Prior to the placental trauma experiments, the sensitivity of pregnant rabbits to thromboplastin extracts was determined. This was done because earlier work with the mouse had shown that the sensitivity to placental extracts increased twofold to threefold as pregnancy progressed toward term (7). Because of the bearing on the present experiment it was desired to find out whether there is a similar increase in sensitivity during pregnancy in the rabbit.

Certain refinements were taken into account. To minimize the risk of foreign protein reactions from these injections, the thromboplastin extracts were prepared from the same species, i.e., from rabbit tissues. Furthermore, to mimic as closely as possible the predicted "native extraction" accompanying the placental manipulations, the thromboplastin extracts were prepared from tissues of the pregnant rabbit uterus. The two tissue sources were the maternal placenta and the fetal placenta. In the human, the maternal placenta is reduced to a decidual layer. In the rabbit, these two placental components are of comparable mass, but the vascular supply is quite different.

There is little intrinsic vascularization in the maternal placentas (2); some of these vessels as well as the intervening stroma undergo degeneration and there is fibrin deposition as term approaches (2). Essentially blood free extracts could be prepared from the maternal placentas by removing the blood before extraction; the large vessels that traversed the maternal placenta (to or from the fetal portion of the placenta) could be squeezed until empty or, especially near term, the entire vessel segments could be shelled out. Thus removing the blood before extraction may have reduced the inactivation by a serum antithromboplastin (8, 10); however some of the thromboplastin yielding stroma was doubtless removed also. A final rinsing in saline then rendered the remaining maternal placental tissue essentially blood free. The tissue was ground in a mortar without abrasive and extracted (8). The extract is referred to as maternal placental extract. The final material was obtained as a crude saline extract from the pooled tissues of several placentas.

By contrast the fetal placenta with its profusion of intrinsic vascularization was difficult to free of its contained blood. Such little removal of blood as was accomplished was done before extraction by simply washing the tissue mass in saline after first stripping it free of membranes.

The thromboplastin activity of each extract was measured in a single stage clotting assay as before (8), except that citrated rabbit plasma, rather than human plasma, was used as reagent. Then the extracts were used to determine whether rabbits are more sensitive

TABLE I.—UNITS OF THROMBOPLASTIN PER GRAM OF TISSUE

Length of pregnancy	Rabbit tissue	
	Maternal placenta	Fetal placenta
Thirteen days	500–1000	500
Twenty-eight days	15	150

to these extracts during pregnancy than in the nongravid condition. This intravascular thromboplastin injection experiment, or sensitivity test, was performed twice; in the first experiment with an extract from maternal placentas of 13 days' gestation, and in the second experiment with an extract of fetal placentas of 28 days' gestation.

RESULTS

Sensitivity of pregnant rabbits to placental extracts. Altogether 11 pregnant and 13 nonpregnant rabbits of 26 to 28 days' gestation age were used in testing the toxicity of the two kinds of placental extracts. The extracts were diluted with physiological saline solution to 1 unit or less, per cubic centimeter. Per unit of thromboplastin there was no difference between the toxicity of the maternal placental extract and the fetal placental extract. The minimum lethal dose for the pregnant rabbit was approximately 20 cubic centimeters; this was injected in a single dose as rapidly as possible through a 20 gauge needle. In the comparison of sensitivities, the minimum lethal dose was determined for the pregnant rabbits and for the nonpregnant rabbits. When the maternal placental extract was the reagent, the pregnant rabbits were 2.4 times more sensitive than the nonpregnant ones; when the fetal placental extract was the reagent, 2.8 times more sensitive. Thus the pregnant rabbit was two to three times more sensitive to thromboplastin extracts than was the nonpregnant one.

The rabbits which received lethal doses of these tissue extracts died of a characteristic disseminated thromboembolism of the pulmonary arterial vasculature. It will not be necessary to discuss these further at this time; it will be sufficient to state that in these thromboemboli the fibrin elements were oriented in the longitudinal axes of the vessels, that the cellular components were much reduced and that the thromboemboli were the same whether the animals were pregnant or not pregnant.

TABLE II.—REACTIONS OF PREGNANT RABBITS TO ARTIFICIAL PLACENTAL SEPARATIONS AT DIFFERENT PERIODS OF GESTATION

Days of gestation	12	17	20	23	25	26	27	28	29	30
Number of rabbits	2	3	1	1	3	3	1	2	1	2
Midzonal liver necrosis										
None	2	2							1	
Uncertain		1			1					1
Limited distribution			1	1	1	2		2		1
Extensive lesions					1	1				
Lethal reaction, immediate							1			

Previous work (7) has indicated that pregnancy in mice did not appreciably alter the tendency to liver necrosis among survivors of the injection of tissue extracts. In the above toxicity studies in rabbits, liver lesions were looked for, particularly in those rabbits which survived the tests by a narrow margin of safety. In the entire group, only one pregnant and one nonpregnant survivor was found to have liver necrosis; in each case this was an animal which had exhibited a severe reaction. This is not sufficient information on which to conclude whether or not pregnant animals are more likely to have liver lesions. It is mentioned merely to indicate that a substantial number of animals would be required to decide whether in this respect there is or is not a difference between pregnant and nonpregnant animals.

Thromboplastin yield from placental tissues. From Table I it can be seen that the yield of thromboplastin especially from the maternal placental tissue was decreased near term. This decrease may be in part a reflection of the marked tendency for local necrosis of the substance of the maternal placenta and for fibrin deposits therein near term (2). In these rabbit tissue extracts the decidual layer itself contributed to the maternal placental extract for the reason that a further separation was not made.

The yield was so great that the extract from 0.2 to 0.3 gram of the more potent tissues was

Fig. 1. Liver, widely disseminated lesions; sacrificed at 50 hours after artificial placental separation at 26 days of gestation. ×½.

sufficient to cause death of a 3 to 4 kilogram pregnant rabbit.

Placental separation experiments. The results of these experiments are summarized in Table II.

Most of the animals survived this treatment. In fact, only 1 of 19 died. The others were sacrificed at appropriate intervals and were examined grossly and microscopically. Liver lesions proved to be the most interesting pathological condition. These are discussed first. The subsequent comments concerning the one animal which died are also extensive because it is believed that this one result is of unusual importance and its value must not be judged from the view that it was only 1 case in 19.

In so far as it was studied the course of development of the liver necrosis of the rabbit closely paralleled that in the mouse (6). An apparent species difference was that unlike the lesions in the mouse (6), which were focal (i.e., were without regard to the microanatomy of the liver), the lesions in the rabbit were found to be consistently midzonal (Figs. 4, 5).

Photographs of the gross liver lesions of the animal with greatest dissemination are shown in Figures 1 and 3. The lesions were most frequent and most extensive near the borders of the lobes. A second extensively damaged liver, but an unusual one in that there was an apparent infarct as its chief lesion, is shown in Figure 2. Moderately widely disseminated lesions occurred in two additional rabbits; both are included in Table II under the classification "limited distribution"; some of the others included in Table II, under "limited distribution" had as few as two or three small lesions visible through the capsule. Thus although the occurrence of extensive lesions of the liver was not frequent, there were at least some lesions in most of the animals following the placental separations, provided the manipulations to cause the separations were carried out in the appropriate period of late pregnancy (Table II).

These lesions were difficult or impossible to elicit by placental manipulations during the middle third of pregnancy (Table II). Similarly, although the number of animals is insufficient for a positive statement, it appeared to be difficult to elicit liver necrosis by this method near term.[1] The animals seemed most sensitive to the placental trauma when manipulations were carried out at 25 to 27 days of pregnancy (Table II).

In the liver lesions of more than minimal size, the detailed appearance was that of a fine, whitish reticulum upon a darker background. That this pattern corresponded to the microscopically lobular structure of the liver can be judged from an examination of Figure 3.

Microscopically the necrosis was midzonal with respect to the lobule, Figure 4. The cords of parenchyma cells deep within the lesions were narrow cylinders while the cells making up the boundaries of the lesions were thickened, as can be seen in Figure 5. The sinusoids deep within the lesions were commonly filled with many leucocytes, both mononuclear and polymorphonuclear (Fig. 5).

[1]It is of interest in this respect that in 1 of 2 animals, in which the cervices were ligated at 31 days, thus preventing delivery, comparable liver lesions developed. The liver necrosis was of limited distribution only. These 2 animals were sacrificed at 33 days of pregnancy, i.e., 1 day past term. Delivery occurs ordinarily at 32 days if the reckoning is done according to the custom of counting the day of mating as the first day. At sacrifice in the postmature animal with the liver lesions, 2 of 3 placentas were found to have been separated, presumably by natural but in this case, futile, forces of labor. In the other animal there was no detectable placental separation, all fetuses were still alive, and there were no lesions visible through the capsule of her liver, nor in microscopic sections.

Fig. 2. Liver, with a large infarct as the chief lesion; sacrificed at 25 hours after artificial placental separation at 25 days of gestation. This was an uncommon lesion; some of the more usual lesions can also be seen at the margins of the liver. ×3⅛.

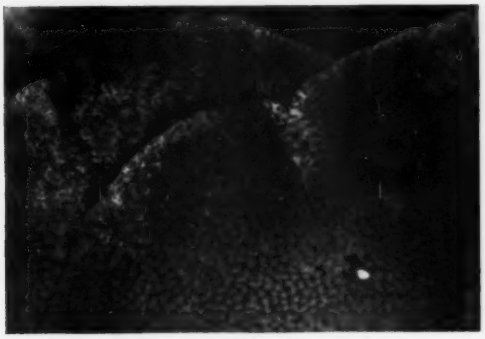

Fig. 3. Liver lesions, enlargement of Figure 1. ×2.

The nuclei of these innermost leucocytes tended to be fragmented if the lesions were more than one day old. In the only rabbit sacrificed at 3 days after the placental trauma, there was a zone of infiltration of leucocytes about the limits of the lesions. In the few lesions observed within less than 1 day after the placental separations (3 animals, 1 each sacrificed at 4, 8, and 12 hours), the cytoplasm of liver cells within the lesions was vacuolated; it was uniformly eosinophilic in those sacrificed after 24 hours. In the early lesions the nuclei of the liver cells were condensed and deeply staining; in the few specimens taken at more than 1 day after treatment, these nuclei tended to blend into the hyaline, eosinophilic cytoplasm. In the 1 animal sacrificed at 3 days, the necrotic liver cells were found to be undergoing resorption from the periphery of the lesions, centripitally. Scarring was not evident. The lesions were entirely midzonal; the larger lesions approached the central veins, but rarely they bordered on them.

The 1 animal that died, did so within 2 minutes of completion of the separation of the last of her 10 placentas. She was the rabbit which was 27 days' pregnant, listed in Table II. As with the other animals, the anesthesia had been discontinued before beginning the placental manipulations. Her final reaction was that of convulsive struggling and gasping, as though for air. Hence this was not a respiratory failure due to deep anesthesia. The heart continued to pulsate for some time. The gross findings in this animal at autopsy were distention of the liver, and dilation of the atrium and ventricle of the right heart. The right cardiac cavities were filled with already clotted blood; this apparently indicated an acceleration of coagulation, since such clots were not usual in animals subjected to autopsy directly after sacrifice. There was no gross pulmonary embolism, the large vessels contained only a thin cord of freshly clotted blood.

There was disseminated, fibrin thromboembolism which was widespread in the pulmonary arterial tree, including medium sized arteries, small arteries, arterioles, and some capillaries.

These thromboemboli were peculiar in that the fibrillar components were densely arranged, parallel to the vascular walls and hence parallel to the flow of the blood stream before the thromboemboli obstructed the blood flow. Particularly in the large vessels, these fibrin plugs were relatively cell free; such erythrocytes as were present were arranged in single or double celled columns and were encased in an eosinophilic matrix which made up the structure of these thromboemboli and took the Weigert stain for fibrin. Numerous leucocytes were also entrapped. Many of the nuclei of the polymorphonuclear leucocytes were distorted in the long axes of the thromboemboli.

Embedded within some of these thromboemboli was considerable débris. It consisted

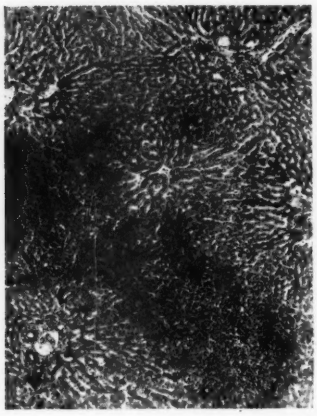

Fig. 4. Midzonal liver necrosis; sacrificed 28 hours after artificial placental separation at 25 days of gestation. ×45.

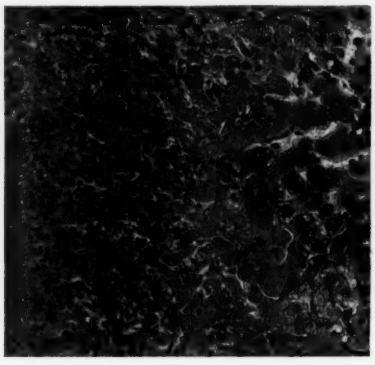

Fig. 5. Detail of midzonal liver necrosis, sacrificed at 28 hours after artificial placental separation at 20 days of gestation. ×140.

both of eosinophilic, amorphous masses and of formed elements. Some of the components of this débris resembled cellular fragments such as can be readily found in the degenerating portions of the maternal placenta of the rabbit near term (see Fig. 10, and cf. Mossman, 2). Such cellular fragments, out of their tissue surroundings, are not sufficiently characteristic for evaluation in text figures. By contrast there were visible a few deported, multinucleated, giant cells; these cells were characteristic of the giant cells of well defined portions of the maternal placenta.

There were some of these well preserved, multinucleated cells entrapped within a thrombo-embolus (Fig. 7). One of these cells is shown enlarged in Figure 8. It was comparable to those multinucleated cells which, as a sheath a few cells deep, make up the walls of the still functional major vessels that traverse the maternal placenta in the rabbit, late in pregnancy (2). These vessels are without an intimal lining other than that made up by these giant cells (2). A section of one of these transplacental vessels, together with an adjoining area of stromal degeneration, is shown in Figure 10. An enlargement of one of the giant cells *in situ* as it projects into the lumen of the placental vessel is shown in

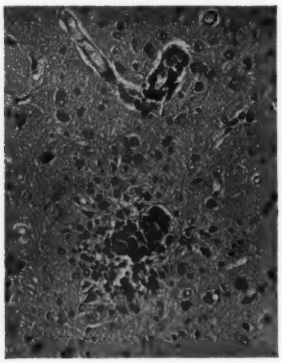

Fig. 6. Small cerebral hemorrhage; sacrificed at 45 hours after artificial placental separation at 30 days of gestation. ×100.

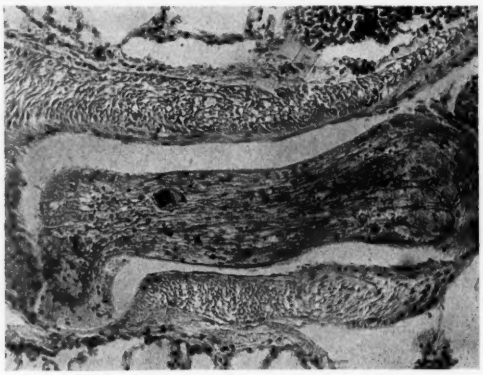

Fig. 7. Pulmonary fibrin thromboembolus, containing 2 deported multinucleated cells from maternal placenta. ×70.

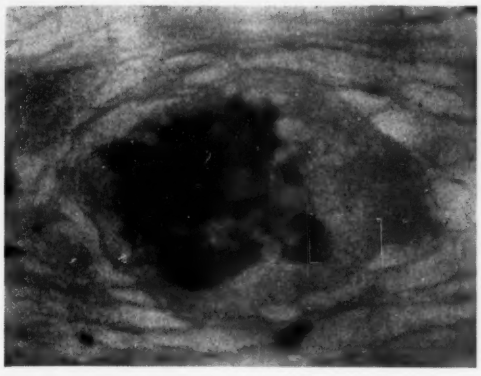

Fig. 8. Enlargement of multinucleated, placental cell which is embedded in the thromboembolus shown in Figure 7. ×700.

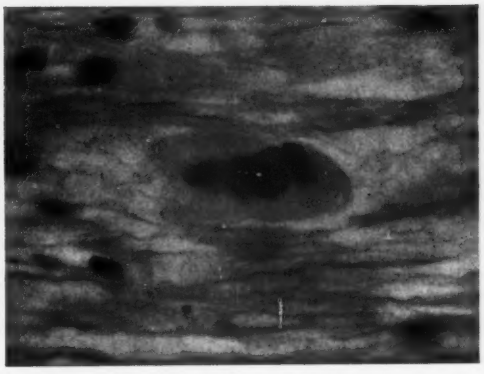

Fig. 9. Additional multinucleated, placental cell embedded (at another level) in the thromboembolus of Figure 7. ×700.

Figure 11; this is for comparison with the apparently similar, deported giant cell of Figure 8.

At another level in the same thromboembolus there was an additional multinucleated giant cell. This cell (Fig. 9) was in a more advanced degree of degeneration than was the similarly deported giant cell of Figure 8. Its cytoplasm was uniformly eosinophilic; the nuclei were condensed and relatively structureless. This deported giant cell resembled closely the degenerating multinucleated giant cells that are located within the substance of the maternal placenta; these are in the regions of the placenta which Mossman (2) interprets to be the remnants of once functional vessels. For comparison with Figure 9, enlargements of two such degenerating giant cells, *in situ* within the maternal placenta, are shown in Figure 12.

The above deported giant cells were found within a thromboembolus. There was also an occasional compact, deeply stained, nuclear mass lodged within the capillary vasculature of the lung, apparently independently of a thrombus formation. It remains undetermined whether these also were deported placental elements.

In contrast to the above predominantly fibrin thromboemboli, there were cellular thrombi also. These were within the smaller branches of the pulmonary arterial tree of

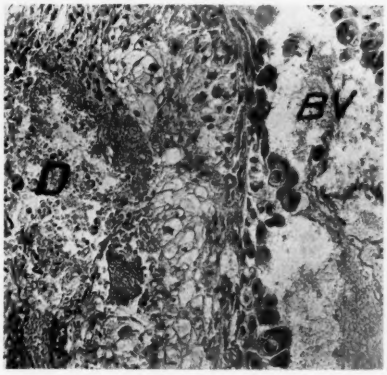

Fig. 10. Portion of maternal placenta, showing multinucleate cells lining a large blood vessel, *BV*, and a degenerating area, *D*, at 25 days of gestation. ×70.

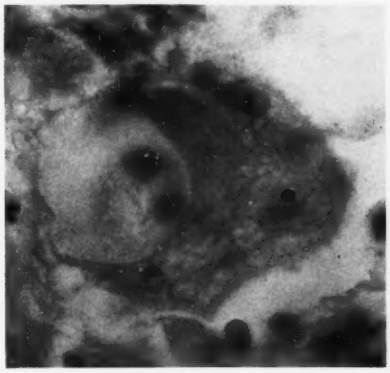

Fig. 11. Multinucleated cell *in situ*, lining large blood vessel of maternal placenta. Compare with Figure 8. ×700.

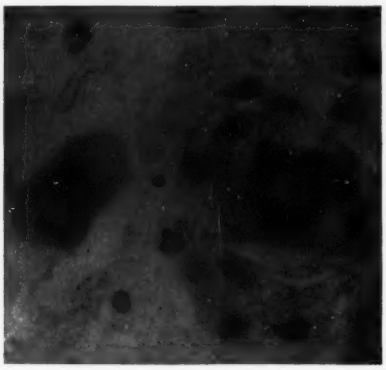

Fig. 12. Degenerating multinucleated cells *in situ* in degenerating portion of maternal placenta. Compare with Figure 9. ×700.

this same animal. The fibrin component of these masses, if present at all, was frequently obscured by the abundance of lymphocytes and of polymorphonuclear leucocytes.

A few isolated fibrin thromboemboli were found also in the pulmonary arterial trees of 3 of the surviving animals (placentas separated at 23, 26, and 28 days of gestation). Each of these animals had some degree of liver necrosis as well.

General observations. In addition to liver lesions and to the pulmonary thromboemboli, there was one of the surviving animals which had a small perivascular hemorrhage into the cortex of the brain. Within this lesion, Figure 6, nucleated cells can be seen phagocytizing the erythrocytes. No associated thrombus was demonstrated. However, only three serial sections of the lesion were available for study. This animal is already included in Table I, for it exhibited liver necrosis as well.

Although it can be stated only provisionally, there appears to be some correlation between the degree of response elicited and the total trauma, as estimated by the total number of placentas separated. Death in the 1 animal occurred after the separation of 10 placentas. Some, but not all of those few animals with the more widespread liver lesions, had undergone several placental separations. Several animals with limited or doubtful liver lesions, had only 2 placental separations.

One of the animals with 10 placental separations in late pregnancy (30 days' gestation) developed only minimal liver necrosis.

During late pregnancy the placentas became separated in the usual anatomic zone of abscission, adjacent to the myometrium. The earlier the period of gestation, the less the tendency for this separation. Greater force in the manipulation was then more likely to result in separation between the fetal and the maternal placentas. This amounted essentially to an intraplacental trauma and was the chief or only result at 17 days or at 13 days of gestation age.

The total blood loss into the lumen of the uterus following the placental separation was usually quite limited.

The separated conceptuses were not usually expelled from the uterus. Some animals near term delivered one or more of the separated conceptuses, still enclosed within the intact membranes as is usual in delivery in the rabbit. This sometimes occurred during the procedure of separating the remaining placentas. One animal, the placentas of which were separated on the thirtieth day of gestation, delivered all of the separated conceptuses during the next day.

DISCUSSION

That particulate matter did enter the circulation in at least one of the above treated animals was demonstrated histologically. Multinucleated cells from the maternal placenta were found within the thromboemboli of the pulmonary arterial vasculature of the mother. That visible elements can thus enter the circulation following placental separations makes the proposition convincing that smaller sized particles, colloidal suspensions, or dissolved substances may also be similarly dispersed into the blood stream. From this assumption it is reasonable to conclude that a "native extraction" of tissue substances from the placenta into the maternal circulation can and does sometimes follow experimental trauma of the placenta.

The possibility that the liver necrosis in the present series of animals may have been the result of infection is minimized by performing the necessary surgery under the ap-

propriate conditions of asepsis. Furthermore, the incipient lesions were demonstrable as early as 4 hours after the placental separations—an unlikely rate of development on the basis of infection even if infection could have been demonstrated this early or indeed at sacrifice after longer intervals. Similarly, it is impossible that the disseminated, pulmonary thromboembolism in the one rabbit which died directly after the artificial placental separation could be ascribed to an infection. This fatal lesion was fully developed within, at most, 5 minutes after separation of the first of her several placentas. This interval was, however, adequate for coagulative deposition of the thromboemboli which were subsequently demonstrated throughout her lungs.

From the nature of the lethal and the sublethal reactions it is implied that the pathologic mechanism was that of intravascular coagulation. Indeed in some of the lesions, this was microscopically visible for there was the deposition of the fibrin thromboemboli. These thromboemboli were of the same characteristic type that were associated with prompt death when the thromboplastin extracts were injected intravascularly into either pregnant or non-pregnant animals (above).

The liver necrosis that followed the placental separations also paralleled that following injection of the tissue extracts. There was similarity with respect to gross pattern, midzonal distribution, microanatomy, and course of development.

Thus the result was the same whether the tissues of the pregnant uteri were extracted and the extract injected into the circulation or whether there was a native extraction from one of the tissues, in this case the maternal placenta, directly into the circulation.

It remains to identify the mediator of the intravascular coagulation. For the laboratory tissue extracts, including placental and decidual extracts, this mediator has been concluded to be thromboplastin (8). Coincidentally, this is the substance which can most readily set the complicated blood clotting mechanism into action. It must not be overlooked that one or more of several coagulation accelerators or initiators (9) might bring about similar results of intravascular coagulation if these were to gain entrance into the blood stream in adequate amount. However, so far as placental or decidual tissues are concerned, thromboplastin is the likely substance. Thromboplastin is present in these tissues in physiologically and pathologically enormous amounts.

The presently reported experiments do not exclude dispersion of material from other tissues of the conceptus into the maternal circulation. Neither are less traumatic or even chronic mechanisms (3) of dispersion excluded. In fact this experiment makes the more plausible that other mechanisms, traumatic or not, severe or mild, acute or chronic, mediated by a specific or by a nonspecific substance, may occur, for it provides visible evidence of dispersion of one potent material from one of the vulnerable portions of the conceptus into the maternal circulation. The possibility is open also that this or another native extraction process may occur repeatedly or progressively during a given pregnancy.

SUMMARY

Pregnancy increases the sensitivity of rabbits at least twofold to intravascularly injected thromboplastin extracts.

By causing placental trauma, several complications of late human pregnancy could be simulated. Liver necrosis could be produced readily in previously normal livers, and the progress of the lesions could be studied.

In 1 of 19 animals, death resulted from disseminated fibrin pulmonary thromboembolism.

These and other reactions were probably due to coagulation intravascularly. There was evidence that following placental damage, material from the placenta might gain access to the maternal blood circulation, and initiate clotting. Thromboplastin is considered to be the chief one of these activators.

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SURGICAL CONSIDERATIONS IN MOBILIZING THE HEPATIC FLEXURE

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MOBILIZATION of the hepatic flexure is required in those cases in which the pathologic condition present indicates resection of the terminal ileum, ascending colon, and full hepatic flexure. Such a situation is found in the presence of cancer, certain types of segmental enteritis, and gangrene of this region due to vascular disease. It may be or often is required when resection of multiple organs for advanced cancer is called for in the region of the transverse colon, ascending colon, pancreas, duodenum, or stomach. Mobilization facilitates examination and judgment as to the possible removal of retroperitoneal tumors. Of extreme importance is the fact that this mobilization gives adequate surgical access to the retroperitoneum, duodenum, pancreas, superior mesenteric vessels, and root of the mesentery. The hepatic flexure may, on occasion, be mobilized in the search for duodenal congenital bands and occasionally for bands involving the ureter. Mobilization of the hepatic flexure not only involves a knowledge of the anatomy but demands a comprehension of the embryologic development and the pathogenesis of the fascial planes involved. It is with this fundamental understanding that this paper is concerned.

The literature has been reviewed in full and dissections have been carried out at autopsy on premature infants of various ages with the permission of the Pathology Department of St. Elizabeth's Hospital.

ANATOMY

The peritoneum about the hepatic flexure is well portrayed in the accepted textbooks of anatomy (1, 4, 5, 6, 7). Perhaps the keenest analysis of its anatomical detail was written by Franklin Dexter over a century ago. When the intestinal canal is still a straight tube in the early embryo, its entire posterior attachment which is uninterrupted is called the dorsal mesentery. The ventral intestinal mesentery is not complete and has a ventral sheet attached to the stomach which terminates at the umbilical vein. Caudally, there is a segment of mesentery containing the umbilical arteries and the urachus. The liver grows out into this ventral mesogastrium. The spleen and pancreas grow out into the dorsal mesentery attached to the stomach and duodenum.

There then follow certain basic intestinal changes which are the key to understanding the adult anatomy about the hepatic flexure. Diagrammatic sketches are inserted to elaborate the fundamental changes mentioned.

The stomach appears as a fusiform dilatation and then rotates so that the original posterior surface becomes the greater curvature, and the original anterior surface becomes the lesser curvature. The dorsal mesogastrium is carried to the left as a developing pocket—the chief anlage of the omental bursa. The small medial opening of this space represents the early foramen of Winslow. This rotation is soon followed by the trace of the great omentum which arises as a diverticulum extending downward just beneath the greater curvature from this anlage. The liver gradually fills most of the ventral mesogastrium except the falciform ligament. The intestinal changes involve a rotation and convolution of the umbilical loop. These changes are made clear in Figures 1 and 2.

The proximal loop convolutes and represents the greater part of the small bowel. The distal loop ascends, rotates, and hence is superimposed on the pancreas, duodenum, and root of the small intestinal mesentery. To the side, the mesentery of the newly formed ascending and descending colon fuses with the underlying parietal peritoneum in the eighth month to form the lamina mesenteria propria by cohesion of these adjacent peritoneal surfaces (Figs. 4, 5).

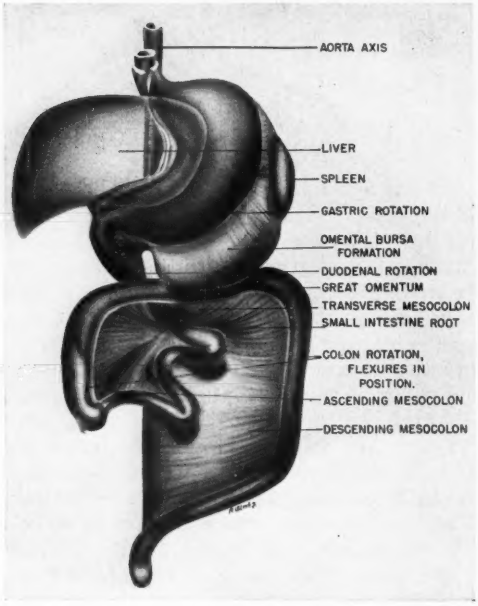

Fig. 1.

The duodenum may be considered to form a loop opposite that of the rotation of the stomach. The first part has a posterior and anterior mesoduodenum. The second part fuses its mesentery with the underlying parietal peritoneum (Fig. 6). In the third part the duodenum lies beneath the transverse mesocolon due to the posterior rotation of the umbilical loop colon. It, therefore, acquires a retroperitoneal course. By these changes, it is evident that the primary axial mesentery attachment to the aorta is lost and is separated into 2 portions. There is 1 for the root of the small intestine descending from the left of the second lumbar vertebra down laterally toward the right sacroiliac joint. There is also a transverse mesentery, that of the rotated transverse mesocolon, which eventually fuses with the downward evaginating greater omentum (Figs. 2, 3). Peritoneal surfaces that become apposed due to the rotation of the intestinal tube become adherent and assume a fascial stratum which is called the fascia lamina propria.

The dissections previously referred to carried out on premature infants revealed that the basic intestinal rotation and mesentery fusion had actually taken place in most instances by the sixth or seventh month of intrauterine life. The layers are very thin but betray variations which explain congenital mesentery malformations which are found in the adult.

For our knowledge of the fascial layers which underly the hepatic flexure, we are indebted to several medical investigations. To

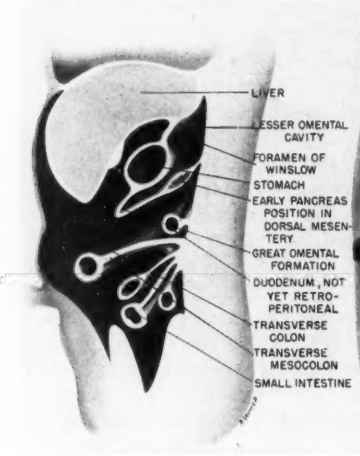

Fig. 2.

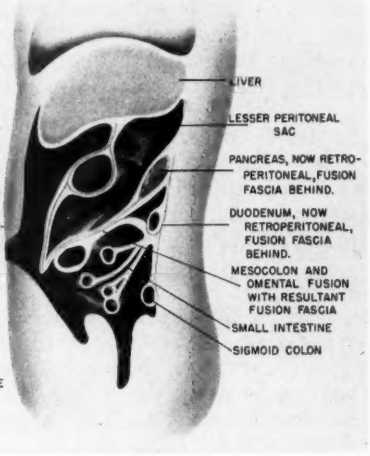
LIVER
LESSER PERITONEAL SAC
PANCREAS, NOW RETROPERITONEAL, FUSION FASCIA BEHIND.
DUODENUM, NOW RETROPERITONEAL, FUSION FASCIA BEHIND.
MESOCOLON AND OMENTAL FUSION WITH RESULTANT FUSION FASCIA
SMALL INTESTINE
SIGMOID COLON

Fig. 3.

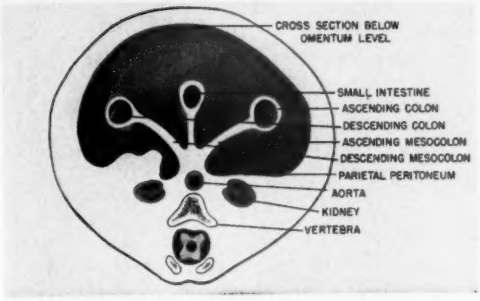

Fig. 4.

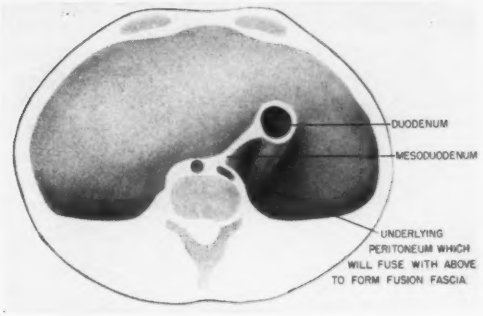

Fig. 6.

Carl Toldt, we owe the establishment of the fact that when enteric mesenteries fuse, a fascia of fusion is formed. As these fusions remain in the adult cavity, they approximate a square foot in extent. Their origin arises as a consequence of the rotations of the colon, duodenum, and stomach previously described. Due to these activities, the mesentery is apposed to underlying parietal peritoneum and the contiguous layers disappear with the formation of fascia lamina propria (Figs. 3, 4, 5, 6, 7). A fascia propria is formed, meaning a fascia of fusion, beneath the ascending, descending, and iliac mesocolons, at the site where the great omentum attaches to the transverse mesocolon and beneath the duodenum and pancreas.

Drs. E. D. Congdon, Blumberg, and Henry have contributed considerably to the knowledge of the fascia of fusion in adults. Their work supplemented that of Toldt in that they did numerous cadaver dissections. They consider fusional fascia as lying on each side of the midline and have divided each into 3 sections. That anterior to the kidney, they called anteroconal. That lateral to the kidney, they called lateroconal. That behind the kidney, they called postconal. On the right side of the body, the anterior renal fascia extends less far cranially than on the left where it extends up beneath the stomach and spleen. Although lying cranial to the transverse colon, there is some support to the view that this dextral fusion fascia extension may be largely colic fascia of fusion. It is felt that the descent of the diaphragm at birth, the rapid relative enlargement of the caudal part of the abdominal cavity after birth, and the assumption of the erect posture of the child may help to explain this caudal migration of the transverse mesocolon. The right anterior renal fascia of fusion, as a rule, is continuous with a fairly well developed layer on the posterior surface of the descending part of the duodenum, and head of the pancreas. The fascia of fusion beneath the kidney level and

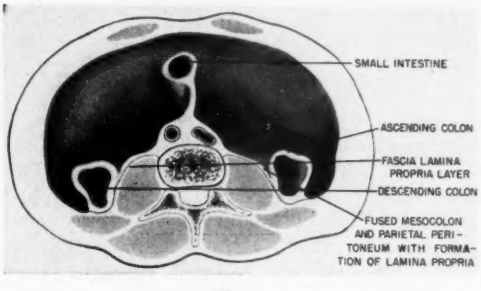
SMALL INTESTINE
ASCENDING COLON
FASCIA LAMINA PROPRIA LAYER
DESCENDING COLON
FUSED MESOCOLON AND PARIETAL PERITONEUM WITH FORMATION OF LAMINA PROPRIA

Fig. 5.

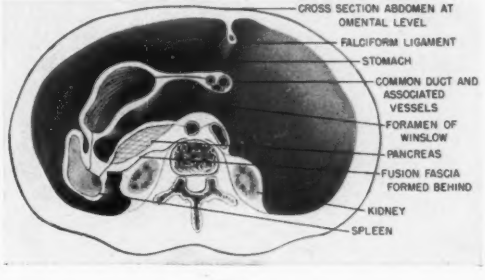

Fig. 7.

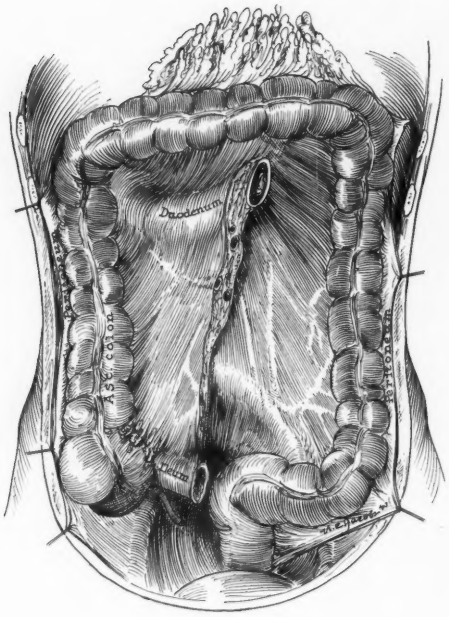

Fig. 8.

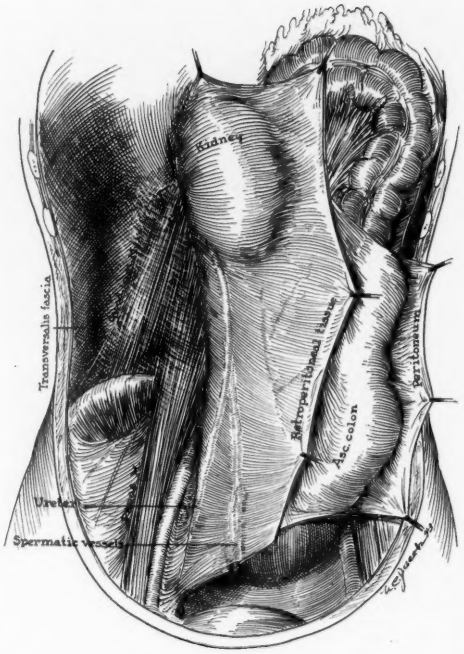

Fig. 10.

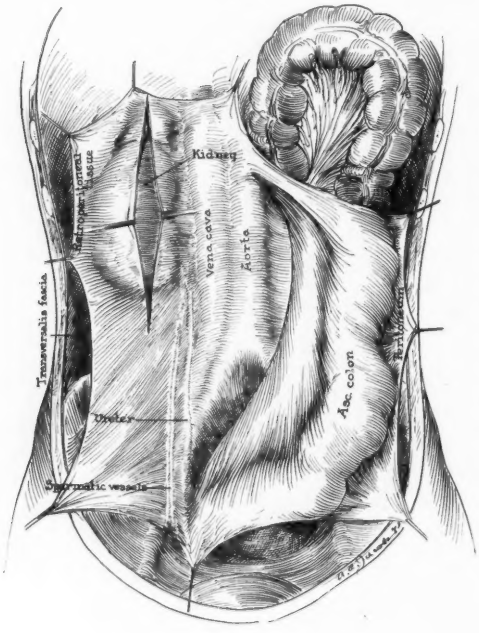

Fig. 9.

extending out laterally beneath the colon segments is spoken of as lateroconal fusion fascia. In a caudal direction, this fascia of fusion extends into what is spoken of as a postconal fascia of fusion. In their series of 234 sections, the lateroconal and postconal fasciae terminated for the most part in the peritoneum just lateral to the paracolic gutter. Sections of mesentery, as reported by Congdon and his co-workers, show a lamina propria in the regions of fused mesenteries in the adult. The colic border is thick at nearly all levels. The middle portions may undergo moderate regressions.

In more recent years, Tobin and his coworkers in Rochester, New York, have contributed greatly to the knowledge concerning the fascia underlying the hepatic flexure by their work in the belief that the entire fascia is divided into 3 layers (8, 9). This concept was suggested by Daseler and Anson in 1943. The first and internal layer for the digestive tube with its vessels and nerves; the

second or intermediate layer for the kidneys, adrenals, ureters, and their associated vessels and nerves together with the aorta and vena cava; and third, an external layer, the transversalis fascia which lines the parietal musculature with its nerves and blood vessels. The intermediate layer may be defined as that tissue between the peritoneum and the intrinsic fascia of the viscera and body wall. The transversalis fascia is defined as that investing fascia on the internal surface of the transversus abdominis muscle. In the adult, the connective tissue between the peritoneum and the body wall forms a continuous lining for the abdomen, pelvis, and either spermatic cord or round ligament.

To attain a better understanding of these discussed strata the reader is referred to 3 diagrams (Figs. 8, 9, 10) contained herein and reproduced through the permission of Dr. Charles E. Tobin. The intermediate stratum beneath the hepatic flexure forms the imbedding matrix for the adrenal, the urogenital stratum, and the larger vessels and nerves, and includes the spermatic or ovarian vein. It encloses the aorta and vena cava in its more medial extension. In the region of the kidneys, this stratum splits into 2 laminae particularly in obese specimens. Local thickening in the ventral lamina forms the renal fascial layer of Gerota. The dorsal condensed lamina encloses the pararenal fat. Above, the ventral lamina encloses the adrenal and fuses with the dorsal lamina. The ventral stratum continues caudally about the spermatic, or ovarian vessel, and the ureter and fuses about the connective tissue about the bladder. At the abdominal inguinal ring, it continues as the internal spermatic fascia of the spermatic cord. The outer stratum is called the transversalis fascia. It is truly not limited entirely to the transversus abdominis muscle, but can be traced medially to the iliopsoas and obturator fasciae.

As one sections the peritoneum lateral to and above the hepatic flexure and separates and releases the omental attachment by lifting the apron and separating it along its relative avascular fascial plane of attachment to the transverse mesocolon, the first step in mobilizing the hepatic flexure is performed. The colon is then mobilized medially between the fascia lamina propria and intermediate fascial layers. It is to be realized that not only the ascending colon can be mobilized in this manner but rather the entire root of the small intestinal mesentery, duodenum, and pancreas can be dissected free and elevated from the subjacent retroperitoneal tissue. At the midline, these structures can be freed as far cephalad as the superior mesenteric vessels.

SUMMARY AND CONCLUSIONS

The preceding considerations present a basis for the comprehension of the existing anatomy of and beneath the hepatic flexure. Mobilization of the hepatic flexure is a surgical step in resection of the right colon as indicated in the opening paragraphs of this paper. More important, however, it gives access to the underlying duodenum, pancreas, kidney, ureter, and vena cava. This access permits the surgical removal of benign or malignant lesions, as indicated, about these organs, particularly of the duodenum, pancreas, and other retroperitoneal structures. In cases of cancer of the duodenum or particularly the pancreas, this procedure enables one to demonstrate that the lesion has not invaded the underlying portal vein or the superior mesenteric vessels. Such invasion contraindicates the radical surgery involved. The ureter and vena cava may be explored by this route although an extraperitoneal route with the same exposure is considered preferable whenever possible. Beneath the duodenum and pancreas a fascial layer of fusion exists and when this layer of fusion is not invaded its removal from the underlying portal vein is possible.

The surgical significance of the hepatic flexure is discussed and the hepatic flexure is described not only on the basis of its adult anatomy but as to the manner of its development.

The underlying fascial planes are described as to origin, location, and development. The knowledge of these findings enables one to proceed surgically along proper fascial planes either to accomplish colon resection or to explore the deeper retroperitoneal vital duodenal and pancreatic areas.

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PITUITARY TUMORS

A PITUITARY adenoma produces two groups of symptoms, those caused by glandular dysfunction and those due to increase in the size of the gland with consequent pressure on neighboring structures. The first group of symptoms, acromegaly, basophilism, and the hypopituitary syndrome is difficult to manage since the results of treatment with hormones or roentgen ray therapy are too often unpredictable. But when the gland begins to increase in size with tension on the diaphragma sellae causing headache, plus changes in the pituitary fossa demonstrable by roentgen film, and compression of adjacent optic nerves with optic atrophy, loss of vision, and diminution in size of the visual fields, then roentgen-ray therapy or surgical intervention becomes imperative. The close anatomic relationship between the pituitary and the optic nerves must always be kept in mind. Preservation of vision should be the primary therapeutic objective. The skeletal and functional changes resulting from disorders of the pituitary gland are distressing. Visual loss is disastrous.

The diagnosis of pituitary enlargement as a cause for visual loss and headache may be suspected by the appearance of the patient and from a careful and detailed history revealing polyglandular dysfunction. The diagnosis is clinched by retinoscopy and the discovery of an atrophic disc. Visual fields for form and color show a unitemporal or bitemporal field cut. Roentgen-ray studies demonstrate the characteristic changes in the sella turcica.

When vision is impaired by a pituitary tumor, immediate steps must be taken to relieve the pressure on the optic nerves before the damage is irreversible. Roentgen-ray therapy or surgery is available. Roentgen-ray therapy requires time to reduce the size of the tumor. Surgery involves the patient in the risk of a mortality.

In deciding whether surgery or roentgen-ray therapy is preferable, a satisfactory rule of thumb is as follows: If the vision in either eye is less than 6/9, especially if optic atrophy is present, and above all if the visual loss has been rapid, the gland should be evacuated by surgical means. If the vision is not less than 6/9 in either eye and if optic atrophy is not clearly evident, roentgen-ray therapy should be given a trial. At the end of the fourth week of this treatment, a visual field for form and color should be obtained. If the fields show expansion, roentgen-ray therapy can be continued with assurance of further improvement. If no increase in the size of the fields is noted, the treatment should be continued, with fields taken at the eighth and tenth weeks. Unless increase in the size of the fields is demonstrable after ten weeks of this therapy, surgical

evacuation of the gland must be strongly considered.

The limitations of the surgical attack upon a primary pituitary tumor should be realized. The adenoma should only be gutted and pressure on the optic nerves relieved. Total extirpation should never be attempted, as it will result in complete pituitary dysfunction and a fatality. Every surgical maneuver directed against the adenoma itself must be intracapsular. Damage to the adjacent hypothalamus and the carotid vessels surrounding the gland produces too serious complications. Therefore, since surgical removal of the gland is never complete, visual field estimations must be done every three months for at least five years after operation, to determine whether or not recurrence of the adenoma is taking place. If the fields are slowly diminishing in size, roentgen-ray therapy may be tried; or if vision has been rapidly reduced reoperation may be indicated. But the surgeon must always remember that his first responsibility to a patient with a primary pituitary adenoma is to preserve vision to the greatest possible extent.

Other tumors are found in the pituitary area of nonglandular origin. Among these is the craniopharyngioma. These tumors arise from squamous epithelial rests of the craniopharyngeal duct. Compression of the gland by the overlying tumor always produces the hypopituitary syndrome. The degree of obvious visible physical changes produced depends upon the age of the patient. Since this is a congenital tumor, short, fat children with definite failure of sexual development are characteristic. But these squamous epithelial rests may not be stirred into activity until adulthood or even advanced years have been reached. In these patients the hypoglandular situation is much less obvious. Fortunately, from 60 to 70 per cent of these tumors are calcified and the distribution of the calcium is such that a diagnosis by roentgen-ray study is easy. Since these tumors originate in the suprasellar area and hence may not deform the pituitary fossa, the presence of a thin shell or even a few flakes of calcium above the sella not only indicates the presence of the lesion but also determines its type. Again, since a craniopharyngioma lies above the sella, the visual field changes may not be a unitemporal or bitemporal cut. Furthermore, these tumors may reach large proportions without producing clean-cut symptoms, especially if the cyst spreads out into the right frontal lobe. Visual loss in children, of the age at which a craniopharyngioma develops, is of little significance to the child. Consequently it may be blind in one eye and with 50 per cent visual loss in the other before it complains or the parents notice that anything is wrong. If these tumors spread upward to block the third ventricle and the foramina of Munro, intracranial pressure is increased with the usual symptoms of headache, vomiting and choked disc.

These tumors seem entirely insensitive to irradiation therapy. Complete surgical removal seems the only hope of a permanent cure. And total surgical removal is difficult and dangerous because the lesion may spread upward and backward to compromise the hypothalamus and downward to entangle itself with the carotid branches.

Meningiomas may arise from the olfactory groove, the inner end of the sphenoid ridge, and the tuberculum sellae. Glandular symptoms infrequently accompany these adjacent tumors since the pituitary gland may not be compressed. The fibroblastomas arising from the olfactory groove obliterate the sense of smell on the ipsolateral side, compress the optic nerve producing atrophy and blindness without distinctive visual field changes, and, as they expand upward into the frontal lobe.

cause change in personality. Localized thickening of the bone of the orbital plate or frontal bone may reveal the presence of such a lesion. But these tumors are among the most silent in their development and may reach a great size before their presence is suspected. The fibroblastomas involving the inner end of the sphenoid ridge cause ocular palsies, compress the optic nerve producing atrophy and bizarre visual fields, erode the ipsolateral clinoid process, thicken the sphenoid bone and orbital roof, and cause unilateral, nonpulsating exophthalmos. Lastly, meningiomas of the tuberculum sellae produce a unilateral temporal field cut and optic atrophy, without changes in the sella or sphenoid bone.

The possibility of complete surgical removal of the olfactory groove and sphenoid ridge meningiomas depends entirely on the size of the tumor, the extent of its attachment to the dura, and the degree to which the adjacent carotid vessels are entangled about the capsule or invade the mass. The tumors of the tuberculum, however, since definite unilateral visual loss plus a temporal field cut appears early, are usually small, do not involve more than the anterior cerebral branch of the carotid, and may be more readily removed in their entirety.

The surgery of the pituitary region then has preservation or restoration of vision as its primary objective. In the removal of these tumors, care must be taken to prevent further damage to the optic nerves and chiasm, to avoid rupture of adjacent carotid branches, and to keep in mind that injury to the adjacent hypothalamus may cause severe and possibly fatal hyperthermia.

The experienced neurosurgeon attacks tumors in and about the sella with due reverence. He knows that all his skill and judgment will be needed if the operation is to be successful. But if he is old at his trade, he further realizes that fortune must favor him. The complete removal of a tumor adjacent to the sella without injury to optic nerves, carotid branches or hypothalamus, leaving a patient without his tumor, but more important, without severe neurologic deficit to hamper his return to economic usefulness, requires surgical deftness and courage, plus a large slice of luck to balance the budget. FRANCIS C. GRANT.

INTRASPINAL TUMORS

WHAT makes the diagnosis of intraspinal tumors so important? Why should every physician keep this diagnosis in mind when he is confronted with unexplained and persistent pain? Or why should a patient's unexplained weakness or atrophy of the muscles or loss or change in sensation arouse the suspicion of this diagnosis? The answer is that the causative factor may be a tumor within the vertebral canal compressing the spinal cord, and relief of pain or complete restoration of function might be accomplished by early operation.

Probably no tumor can create such a variety of pains and disability as can an intraspinal one. Yet the majority of intraspinal tumors are benign, producing disability by direct pressure upon the intraspinal nerves and tracts of the spinal cord. However, since the pressure may interfere with the circulation and nutrition of the spinal cord, irreparable damage may be caused, not by invasion of the cord, but by ischemic and degenerative processes. Hence, early diagnosis and removal are most important.

Little did Gowers and Horsley realize the importance of their contribution when in 1887 they, for the first time diagnosed and successfully removed an intraspinal tumor. It is said that as early as Hippocrates, operations on the spinal column had been advised for the relief of pressure on the spinal cord subsequent to

trauma. Hildanus also urged that this be done, but it was not until 1814 that Cline successfully removed the arch of a compressing vertebra. Little attention was paid to this type of surgery until William McEwen operated upon a man in whom complete paraplegia had developed after an injury to his back. Eight weeks after the injury McEwen examined the patient and then operated, relieving compression of the spinal cord by removing the fragmented arch of the vertebra. This was done in 1885. In 1886 Gowers, who had followed with interest the relief of symptoms subsequent to McEwen's operation, urged that intraspinal tumors be removed, and called attention to the fact that the symptoms which they produced were caused by compression developing slowly over a long period. It was not until 1887, however, that a patient was seen who, when examined by Gowers, was found to have evidences of compression of the spinal cord with pain and motor and sensory changes, and the diagnosis of intraspinal tumor was made. Sir Victor Horsley then performed the first successful removal of an intraspinal tumor.

The difficulty in diagnosis of intraspinal tumors stems from the slow, insidious onset and often intermittent occurrence of the symptoms. These factors of course are confusing, because the symptoms often simulate those of certain degenerative diseases of the spinal cord, and may be misleading. The pain of intraspinal tumors may occur in certain areas in which a coincidental pathologic process is found and removed, without relief of pain. This has happened in cases of disease of the gallbladder, ovarian tumors, fibromas of the uterus, appendicitis, thoracic tumors, bony lesions of the extremities and countless other coexistent lesions which should be removed.

In addition to the painful syndromes which prove to be stumbling blocks in the diagnosis of intraspinal tumors, there are certain motor and sensory manifestations which also confuse the picture. Sensory changes in the extremities associated with certain blood dyscrasias have been identified with degenerative changes of the spinal cord. In all cases "creeping paralysis" associated with anemias and syphilis of the central nervous system should be avoided as a diagnosis until an intraspinal lesion has been ruled out.

Intraspinal tumors vary as to symptoms depending upon the level at which they are compressing the spinal cord. Tumors which develop high in the cervical region also may cause symptoms similar to those of intracranial tumors, and may be accompanied by choked discs. So-called tumors of the foramen magnum may cause symptoms predominantly cerebral or spinal, depending upon the direction of the extension of the tumor. Tumors which occur in the cervical portion of the spinal cord may simulate inflammatory and neoplastic lesions of the brachial plexus. They frequently masquerade as the scalenus anticus syndrome, with or without roentgenologic evidence of cervical ribs. The syndrome of herniated intervertebral discs in the cervical region has received much attention in recent years, and may be confused with the symptoms of an intraspinal tumor in the same region.

Intraspinal tumors in the thoracic or dorsal region usually affect the thoracic and abdominal contents, and create symptoms associated with such diagnoses as "pleurisy," "mediastinitis," upper abdominal lesions such as "cholecystitis," "pancreatitis" and "ileitis," and lower abdominal lesions such as "appendicitis," "cystic and neoplastic oophoritis," "uterine fibromyomas," "colitis" and "hemorrhoids." In such instances diagnosis is, of course, associated with palpable or evident pathologic lesions which also are present. The

interesting and pertinent reason for calling attention to these coexisting lesions is not to question the diagnostic acumen of the physician, but to suggest that should a patient's pains persist after removal of evident lesions, the presence of intraspinal lesions should be suspected.

Intraspinal tumors in the lumbar and lumbosacral regions probably are the most confusing in respect to the symptoms they cause. The reason for this is that the spinal cord terminates in the lower thoracic and upper lumbar region, and the intraspinal contents from there downward consist of individual nerve roots. Tumors may grow to extensive size in this region before the symptoms become sufficiently acute to necessitate investigation. Here, also, the attention in the past few years has been focused upon herniation of intervertebral discs, particularly the ones between the fourth and fifth lumbar and the fifth lumbar and first sacral vertebrae.

In fact, the symptoms of the syndrome of herniated intervertebral disc are so similar to those of intraspinal tumor that no clear line of demarcation can be drawn. When it is considered that both intraspinal tumors and herniated intervertebral discs compress the nerves of the cauda equina, it is apparent that a state of confusion in respect to the two will always exist. Therefore, in order to arrive at a differential diagnosis, studies of the hydrodynamics of the cerebrospinal fluid and chemical examination, contrast media and careful neurologic examination are of value, and play a part in solving the problem of pain and disability in the lower extremeties as well as in the other regions of the body.

Roentgenologic examination of the vertebral canal is one of the most important parts of the general survey, because evidence of erosion, thinning, calcification, and overgrowth of the bone frequently is indicative of the underlying pathologic process. Probably the most important part of the examination is careful evaluation of the changes in motion and sensation. Changes in reflexes and atrophy of muscles individually and in patterns sometimes lead to a solution of an otherwise complicated problem. Not the least part of the examination is the careful taking of a history. For instance, the statement that the patient was awakened from a sound sleep in the early morning hours by a pain which could be relieved by getting up and sitting in a chair may immediately focus the attention of the examiner and make an early diagnosis possible. While the majority of intraspinal tumors are benign, metastatic lesions do occur, and for that reason a careful general examination should be carried out. Also, associated blood dyscrasias or constitutional disturbances should be evaluated, if they are present.

Since the days of Sir Victor Horsley the surgery of intraspinal lesions has been greatly simplified. Asepsis, anesthesia, antibiotic agents, hemostatics and technical assets such as the electrosurgical unit have combined to render operation on the spinal column more nearly exact and associated with a markedly lessened risk. WINCHELL MCK. CRAIG.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE excellent two volume *Atlas of Roentgenographic Positions*[1] fulfills in a very satisfactory manner the purpose for which it was intended, i.e., "a practical reference book." As stated in the title it is an atlas of positioning, and exposure technique receives no consideration. X-ray technicians, both beginners and veterans, will find multiple answers to their everpressing question, "How can we best demonstrate the requested anatomical structure?" For example 8 different positions are described and illustrated showing lateral projections of the femoral neck, and 12 different positions showing the pars petrosa of the temporal bone.

The author lists the different positions both by the projection used and by the originator's name. The Chamberlain-Towne position, however, is not listed under the oblique, anteroposterior projection of the cranium. Certain illustrations do not fit the described projections, e.g., 2 of the 3 illustrations on page 319. Certain line drawings, as on page 344, though properly described in the text are incorrectly drawn. One might also question the propriety of recommending sight development of paranasal sinus films. Sufficient anatomical drawings and text have been included to give the student an adequate background for radiographic positioning.

Volume 1 begins with a timely orientation chapter called "Preliminary Steps to Roentgenography." A glossary of over 1,000 words commonly used in roentgenography is included in this volume. An extensive bibliography and a complete index in each volume add considerably to the value of the atlas. This publication is recommended as a valuable addition to the roentgenographic library of every x-ray department and especially to those departments having student technicians.

ROBERT BURNS LEWIS.

AN excellent study of the physiologic and pathologic changes of the ureter as demonstrated by retrograde and intravenous pyelography is presented in the volume entitled *Die Pathologie des Harnleiters im Roentgenbild*[2] which is recommended to all students of urology and roentgenology.

While nothing new appears to be added to our understanding of ureteral anatomy and physiology or of ureteral changes in disease processes, the subject is presented in such a clear and concise manner that it can readily serve as a reference guide in the interpretation of films. There are 71 illustrations; the majority of these are ureteropyelographic reproductions. Short case history abstracts and roentgenologic legends add to the value of the illustrations.

The author has given careful consideration to the interpretation of the form and behavior of the ureter under numerous circumstances. The ureter, serving merely as a conduit from renal pelvis to bladder can be considered anatomically as a single unit, but in a physiologic and pathologic sense it cannot be divorced. It must be adjudged a partner in a complex system, the vital link between the upper and lower urinary tracts, in which relationship physiologic variations and diseases in one organ are reflected in the others. In diagnostic and differential diagnostic roentgenologic work the ureter per se plays a most important role.

The text is divided into 4 parts. Part 1 presents a general discussion of the anatomy, physiology, and pathologic physiology of the ureter. The diagnostic methods of intravenous and retrograde pyelography are commented upon. Part 2 deals with congenital variations and the obstructive uropathy (urethral, vesical, intraureteral, and extraureteral). Part 3 covers infections in the urologic tract. Part 4 contains an interesting exposition of dynamic functional changes (hypotony and atony) in the ureter associated with such conditions as nephroptosis, hydronephrosis, uretheral stone obstructions, solitary kidney.

Two hundred references are given; the majority are to German authors. The paucity of British and American authors and dates of references indicate the effect of war on the exchange of foreign literature.

The format, the quality of the printing and excellent texture of the paper, and clarity of the roentgen reproductions deserve words of praise for the Thieme firm of Stuttgart.

CHARLES A. W. UHLE.

THE very carefully worked out treatise on the use of diathermy in the surgical treatment of tuberculous sinuses, *Die elektrochirurgische Behandlung der Tuberkulose*,[3] is excellently documented and illustrated. Many cases of sinuses in various parts of the body are described in detail. The author stresses the importance of using a particular strength of coagulating current which will heat the tissues without producing an eschar. He has not sufficiently stressed the fact that practically all such tuberculous sinuses

[1] ATLAS OF ROENTGENOGRAPHIC POSITIONS. By Vinita Merrill. Vols. 1 and 2. St. Louis: The C. V. Mosby Co., 1949.

[2] DIE PATHOLOGIE DES HARNLEITERS IM ROENTGENBILD. By Dr. Anton Thelen. Stuttgart: Georg Thieme, 1949.

[3] DIE ELEKTROCHIRURGISCHE BEHANDLUNG DER TUBERKULOSE. By Heinrich Bruegger. Stuttgart: Georg Thieme, 1949.

are caused by some underlying pathology which must be cleared up before the sinuses will heal permanently. JEROME R. HEAD.

THE excellent book *Die Erkrankungen der endokrinen Druesen*[1] presents a comprehensive survey of our present knowledge concerning the role of the endocrine system in disease. General physiologic, pathologic, and therapeutic considerations are discussed in one section. In a larger section chapters are devoted to the hypophysis, pineal gland, thyroid, parathyroid glands, the thymus, suprarenal glands, the gonads, the pancreas and to the spleen, liver and salivary glands.

Use of a very extensive bibliography is facilitated by references in the text with the sources listed at the bottom of the page. WALTER H. NADLER.

THE book entitled *A Textbook of Neuropathology; with Clinical, Anatomical and Technical Supplements*[2] is written by a practicing neurologist who, using neurology and neuroanatomy as orienting mileposts, weaves clinical data into the discussion of pathologic changes in a given condition. The result is that not only is it easy to read, but the concept of neuropathology gained by readers is that of an integral part of neurology as a whole, and not merely a review of what might be seen under the microscope.

This book is straightforward throughout. The author has, on controversial subjects, presented admirably the opposing views without entering into long discussions on points that are still theoretic. The work includes, besides the usual subjects treated in texts on neuropathology, informative chapters on malformations of the nervous system, deformities and artefacts, adventitious and metabolic substances, muscular disorders and related states. In the second chapter the author discusses in a general way the manner in which the components of the nervous system should be removed at necropsy in order to obtain from them the most information, and he considers methods of fixation of the tissue. He then presents an outline of what can be seen with the various stains. For the reader who is interested in histologic techniques, the author has included as the last chapter of the book concise but complete step by step instructions for the preparation of gross specimens, neurologic staining methods and impregnation techniques. General pathologists, whose work in neuropathology may be only occasional, and laboratory technicians will regard this chapter as a commendable addition to the book.

The section on neoplasms of the nervous system is clear and direct; its objective is to simplify the subject for the elementary student rather than to confuse him with its many perplexities. The author has subdivided neoplasms of the nervous system according to their sources of origin, as for example: (a) neoplasms of neuroepithelial origin; (b) neoplasms arising from the skull and vertebral column, the meninges, the meningovascular prolongations within the brain and spinal cord, and the nerve roots and peripheral nerves; (c) the neurocutaneous states (tuberous sclerosis, von Recklinghausen's disease); (d) neoplasms arising from the anterior lobe of the hypophysis and its anlage; (e) neoplasms of a teratomatous, teratoid, dermoid and epidermoid character; (f) metastatic tumors; (g) pathologic states resembling or related to the neoplastic state; leucemia and Hodgkin's disease. This grouping provides the student approaching the subject for the first time with a logical and orderly framework on which to build his comprehension of a difficult subject. The practicing neurologist or neurosurgeon may consider this chapter somewhat sketchy.

Included in the book to serve as orienting references are a neuroanatomic supplement and a clinical supplement. The latter comprises brief reviews of 114 syndromes, many of which are designated by eponyms and consequently cumbersome to remember.

By the inclusion of the material mentioned above, and the integration of clinical neurology with the pathologic changes, the author succeeds in producing a text which stands out as a well integrated unit dealing with the broader aspects of neuropathology. The reviewer warmly recommends Dr. Lichtenstein's text not only to medical students and graduate students in neurology, psychiatry, general pathology, and neurologic surgery (for whom the book was primarily intended), but to the specialist in neuropathology as well. The latter, unless he is in daily contact with clinical neurology, will find that this presentation of neuropathology from a neurologist's point of view will refresh his memory regarding many clinical aspects with which his work is so inextricably intertwined. HENDRIK J. SVIEN.

SHORTLY after World War I, Geoffrey Keynes published a text entitled *Blood Transfusion*.[3] This was essentially a report based upon his own experience and covered 136 pages. During the intervening years with the many new problems of serology and multiplicity of techniques this subject has expanded to a considerable extent. Great impetus was also given to it during the recent World War. As a result the author felt that the most efficient manner in which to bring the subject up to date was through the aid of a number of collaborating writers, each a man of experience in a particular aspect of this ever broadening field. The new 565 page text *Blood Transfusion* is therefore the work of 8 contributors, the editor restricting himself to the section concerning the history of blood transfusion.

In general this text is essentially a compilation of data gleaned from the world medical literature inter-

[1] DIE ERKRANKUNGEN DER ENDOKRINEN DRUESEN. By Prof. Dr. Adolf Oswald. Bern: Hans Huber, 1949.

[2] A TEXTBOOK OF NEUROPATHOLOGY; WITH CLINICAL, ANATOMICAL AND TECHNICAL SUPPLEMENTS. By Ben W. Lichtenstein, B.S. M.S., M.D. Philadelphia, London: W. B. Saunders Co., 1949.

[3] BLOOD TRANSFUSION. By H. F. Brewer, Richard Ellis, R. I. N. Greaves, Geoffrey Keynes, F. W. Mills, R. Bodley Scott, Anthony Till, and Lionel Whitby. Edited by Geoffrey Keynes. Baltimore: The Williams & Wilkins Co., 1949.

spersed with reports from personal experience. The subject matter is presented in sections, each contributor tending to use a somewhat chronological approach with recurrent reference to the opinions of others as the particular section is traced through its development to the exposition of its present day status. An extensive bibliography at the end of each section makes the text a handy cross reference guide.

Short sections covering the clinical indications for, as well as the complications of, transfusion precede the more theoretical section on blood grouping. Storage and preservation of blood and the techniques of transfusion are well covered. The section on transfusion of infants deserves special mention. The remainder of the text covers much of the commonly known routine practices and data to be found in all well organized blood transfusion services. Although this book's greatest appeal will be to those interested in the field of transfusion, it also will serve as a satisfactory source of reference to those who wish a complete medical library. WALTER W. CARROLL.

THE author of *Early Carcinoma of the Uterine Cervix*[1] is one of the most experienced with the use of the colposcope and throughout his work he correlates the colposcopic appearance of cervical lesions with their microscopic characteristics. Based upon his experience he advocates the routine use of this method of diagnosis. The Schiller test, vaginal smear, and biopsy are discussed for screening patients for cancer.

Classification of epithelial changes in the cervix is attempted but the one given is too complex for routine use. Although a more simple classification is suggested at the end of the monograph, the more complicated one is employed throughout the description.

The author describes the growth of cancer as occurring in two phases. In the first phase carcinomatous epithelium spreads within the epithelial layer. In the second phase genuine carcinomatous invasive growth occurs. The author adds that these two phases do not always follow each other. Invasion may start simultaneously with the beginning intraepithelial growth. Two cases are presented in which invasive downgrowth originated from the basal epithelium beneath a normal looking surface. From the surface or preinvasive carcinoma, a genuine cancer occurs simultaneously in several places, a multicentric origin.

Evidence is presented to indicate that what the author terms "increasingly atypical epithelium" continues on to genuine invasive cancer. However, he discusses 2 cases in which this type of epithelium reverted to normal without developing into cancer, and properly raises the question as to whether a change which can be reversible should be called by the ominous name, carcinoma.

In those cervices that have atypical cell changes within the epithelial layer, the author points to the comparatively well preserved stratification and the high degree of maturity of the epithelium as a sign of noncarcinomatous changes. On the other hand, he believes that the occurrence of individual giant nuclei, and giant cells, and even frequent mitotic figures in the basialis are not sufficient evidence to make the diagnosis of carcinoma.

The long latency period shows how chronic a disease cancer may be. Nevertheless, a few cases are described by the author which show that it is not absolutely necessary for the atypical cervical epithelium to appear several years before the development of carcinoma.

He states that the distribution of genital carcinoma as to age groups and pregnancies leads to the conclusion that the normal sexual function and especially gestation take part in the origin of cervical cancer and shows that completely physiologic occurrences may have an essential influence on the formation of cancer.

He concludes that further research will find in the virus theory a solution to the cancer problem.

While it is not possible to agree entirely with the author, the work brings forth evidence concerning certain facts of cervical carcinoma that are enlightening, pertinent, and much needed. To the clinician and the investigator this monograph is timely and worth while. JOHN I. BREWER.

THE monograph[2] by Professor Karl-Ewald Herlyn on plastic surgery is largely a presentation of case reports, mostly of posttraumatic deformities resulting from World War II. A large percentage of these cases are limited to extensive war injuries about the face.

The cases are illustrated with preoperative and postoperative photographs which are very clearly reproduced. A number of the surgical procedures are illustrated diagrammatically. Most of these cases have been repaired with multiple stage procedures of tube or rope grafts. The end results in the majority of the cases appear unfinished, and it is probable that a great deal of improvement could be attained by "smooth-up" operations. Apparently not as much importance has been given to color and texture matching of the skin as might have been, but there is no question that the final results show much improvement over the original condition. No outstanding new techniques are presented.

W. M. ADAMS.

THE seventh edition of *A Descriptive Atlas of Radiographs*[3] by A. P. Bertwistle, in the words of the author, is "an attempt to portray, as far as pos-

[1] EARLY CARCINOMA OF THE UTERINE CERVIX; PATHOGENESIS AND DETECTION. By Hansjakob Wespi, M.D. Translation by Marie Schiller, Ph.D. Foreword and Survey by Walter Schiller, M.D. Rev. and enl. ed. New York: Grune & Stratton, Inc., 1949.

[2] DIE WIEDERHERSTELLUNGS-CHIRURGIE; INSBESONDERE DIE VERWENDUNG DER ROLLAPPENPLASTIK. By Prof. Dr. Med. Karl-Ewald Herlyn. Stuttgart: Georg Thieme; New York: Grune & Stratton, Inc., 1949.

[3] A DESCRIPTIVE ATLAS OF RADIOGRAPHS; AN AID TO MODERN CLINICAL METHODS. By A. P. Bertwistle, M.B., Ch.B., F.R.C.S. (Ed.). 7th rev. enl. ed. St. Louis: The C. V. Mosby Co., 1949.

sible in the space available, as many of the normal and abnormal conditions that are met with in practice. It is written by a clinician for clinicians. It is primarily intended for the use of the clinician who desires to know what x-rays are capable of revealing to him." In that respect, the book fulfills its purpose.

With a minimum of technical detail, the author describes the various methods by which the anatomical systems may be studied radiographically. The book contains a fairly accurate history of x-ray diagnosis outlined by systems.

The remainder of the book is comprised of reproductions of radiographs. Each reproduction is accompanied by a short history together with a description of the x-ray findings. The discussions of the radiographs are on the same pages of the book which is a great aid. The reproductions are positive images which lead to considerable confusion in comparing the reproductions with radiographs in an x-ray viewing box. This might be a serious handicap to the untrained roentgenologist. Some of the radiographs have not been reproduced clearly. This has been corrected by sketches of the reproductions in some instances. In addition, the author's method of "silhouette radiography" described in the book has aided greatly in making the reproductions more clear cut and diagnostic.

This book contains some inaccuracies and obscurities but fairly well fulfills its intended purpose as a clinical guide. S. H. SQUIRE.

THE universal acceptance of *Operations of General Surgery* by Thomas G. Orr[1] is amply evidenced by the appearance of the second edition in the short period of 5 years. The illustrations numbering 1,396, step by step, on 570 figures in the first edition have been increased to 1,700 on 721 figures. Revisions have been made throughout the chapters. The outstanding additions have been in the chapters on the thorax and respiratory system, circulatory system, digestive system, and congenital anomalies. The recent notable contributions in technique for esophageal atresia, tracheoesophageal fistula, atresia of the bile ducts, intestinal atresia, anomalies of the aortic arch, pulmonic stenosis, coarctation of the aorta, vagotomy, total gastrectomy, portocaval shunts, splenorenal anastomosis, pulmonary lobectomy, decortication for hemothorax and acute empyema, resection of the upper rectum and lower sigmoid with end to end anastomosis, the Wangensteen loop colostomy and closure, and the Dennis ileostomy are all clearly illustrated and discussed in their essentials. The illustrations throughout the text are graphic and prepared by outstanding medical artists. A complete bibliography is included at the end of each chapter.

The volume can be regarded as a valuable and complete presentation of modern surgical techniques as advocated by leading authorities, and the author is to be congratulated on a difficult task superbly accomplished. This text will prove to be a valuable addition to the library of the student, intern, resident, and surgeon. CLIFFORD D. BENSON.

THE text of *Fundamentals of Otolaryngology*[2] by Lawrence Boies is arranged in a systematic and simple style, the work of men who have had actual teaching experience. The book is particularly valuable as a text for students in ear, nose, and throat.

The illustrations are excellent and the applied anatomy, physiology, etiology, pathology, diagnosis and treatment are taken up in logical order.

Practical prescriptions are also offered for the treatment of otolaryngological disorders.

HENRY M. GOODYEAR.

THE 391 page book, *Illustrations of Surgical Treatment; Instruments and Appliances*[3] first published in 1939, revised in 1942 and again in 1949, is, as the author states, primarily for assistance to students preparing for examinations, house surgeons, and recent medical school graduates. Without entering into undue detail, Dr. Farquharson has in Part 1 described and illustrated with excellent photographs and drawings the standard apparatus and method of use for intravenous infusions and transfusions.

Parts 2, 3, and 4 which comprise more than two-thirds of the book, describe and illustrate the method or methods of closed reduction, traction, plaster, splint or internal fixation suitable for each of the more common fractures or dislocations. The management of these injuries of the spinal column, ribs, shoulder girdle and upper extremities, and pelvic girdle and lower extremities is discussed and depicted in a clear, concise manner. The management of a few other orthopedic conditions, such as the more common forms of osseous tuberculosis, congenital dislocation of the hips, deformities of the feet, stiff knees, semilunar cartilage injuries, and tennis elbow, is included in these sections. It is this portion of the book dealing with fractures and dislocations which makes it a practical manual for all who are interested in traumatic surgery. One may not always agree with the method of treatment described, but always the rationale and principle are sound.

The appendix in an orderly fashion illustrates not only the instruments and appliances which are part and parcel of every operating room but also special instruments and appliances required in the following fields of surgery: (1) fracture and orthopedic surgery, (2) esophageal, gastrointestinal, biliary surgery, (3) genitourinary surgery, (4) thoracic surgery.

Although in the original preface, Mr. Farquharson defends the title of his book, possibly this manual

[1]OPERATIONS OF GENERAL SURGERY. By Thomas G. Orr, M.D. 2d ed. Philadelphia and London: W. B. Saunders Co., 1949.

[2]FUNDAMENTALS OF OTOLARYNGOLOGY; A TEXTBOOK OF EAR, NOSE AND THROAT DISEASES. By Lawrence R. Boies, M.D., and associates. Philadelphia and London: W. B. Saunders Co., 1949.

[3]ILLUSTRATIONS OF SURGICAL TREATMENT; INSTRUMENTS AND APPLIANCES. By Eric L. Farquharson, M.D., F.R.C.S.(Ed.), F.R.C.S. (Eng.). With a foreword by the late Sir John Fraser, Bt., K.C.V.O., M.C., M.D., Ch.M., F.R.C.S.(Ed.). 3d ed. Baltimore: The Williams & Wilkins Co., 1949.

would be more widely acclaimed and used were it known by another name, such as "Illustrations of Fracture Treatment, Venoclysis, and Surgical Instruments." PAUL R. LIPSCOMB.

IN the book *Varices del miembro inferior*[1] by Alberto E. Laurence, the anatomical, physiological, and pathological considerations are well presented. In his clinical studies the author describes most of the conventional procedures accepted by American surgeons. Each chapter is accompanied by excellent illustrations.

Particular recommendations are given concerning the technique of ligations combined with injections. This has been the procedure preferred by the author. Injection into the emptied vein and early ambulation have been the key to the author's success.

This book is a worthy edition to the library of any surgeon treating varicose veins and their complications. PEDRO A. GARCIA.

ONE of the serious problems in teaching the graduate student has always been the discovery of ways of keeping him in touch with the vast material of current literature. Professor Ian Aird of the London Postgraduate School has attempted an unusual method of meeting this difficulty in his *Companion in Surgical Studies*.[2] He opens his introduction with the statement that the student must have ready and rapid access to the ever-growing canon of established fact. The author "has tried to predigest the written work of others by the enzymes of personal experience," both for the trainee in general surgery and the apprentice in more restricted fields.

For this purpose Professor Aird has written a book indexed along the lines of standard surgical texts with which it is intended to be read. In its 1,000 pages, entirely unillustrated, the author provides a running commentary to crystalize current literature. While referring chiefly to American and British material, it is refreshing to find not a few from European sources, with which we are often less familiar. In all, the references average more than 4 to each page.

The marks of 20 years' experience as a teacher are everywhere apparent, and the result is a very helpful and provocative volume for both graduate student and instructor of graduate students.

The whole field is covered except for orthopedic surgery, which is purposely omitted. The result has been a well digested summary of present-day knowledge in condensed and readable form. A few apparent omissions may be noted, but these will probably be amended in succeeding editions. For instance, in the discussion of complete rectal prolapse, the Rehn-Delorme repair and modifications are not mentioned. Sliding hernia is described very briefly but there is no reference to some of the techniques which are used in this country and which improve the results. In the pages on peptic ulceration, which are particularly well presented, the defunct theory of Rosenow is still mentioned.

The volume makes a peculiarly valuable addition to surgical libraries and will be of immense assistance to graduate students and graduate instructors.

W. F. GILLESPIE.

THE frequent use of blood plasma transfusions in modern medicine makes the volume entitled *Blood and Plasma Transfusions*[3] of great practical value to the entire medical profession. It not only serves as an adequate review of the subject for the busy clinician, but also is a helpful manual for those whose duties are concerned mainly with the technical methods and problems encountered in the every day management of an active blood transfusion service.

The chapter devoted to a discussion of the blood groups and types serves to classify and explain the agglutination reactions which form the bases for the various blood types and subtypes. The material is presented in a concise form which succeeds in providing the essential information without becoming telegraphic in its quest for brevity.

The section which includes a general discussion of the Rh-Hr blood types is necessarily and admittedly more detailed, but manages to avoid the controversial aspects of the problem. The chapters on the indications for transfusions, or adverse transfusion reactions, and on the transmission of disease through transfusions are of especial interest to the clinician, while most of the remaining space is given over to problems which are of interest primarily for the laboratory worker. ORVILLE F. GRIMES.

THE rapid succession of new antibiotics which have been developed since the advent of sulfanilamide has demanded development of a technique of evaluation of the effectiveness of the drugs and of any toxic effects upon the human body. When it became apparent that streptomycin had value in the treatment of tuberculosis, a supply of it was given to a Streptomycin Committee of the Trudeau Society, of which Dr. H. McLeod Riggins is chairman. This was used on selected cases in various clinics and the reports were carefully kept and carefully tabulated. *Streptomycin and Dihydrostreptomycin in Tuberculosis*[4] is a collection of the reprints which this committee has published from time to time over the past 3 years. It presents in detail all of the work which this committee has done on streptomycin and dihydrostreptomycin, and is a valuable

[1] VARICES DEL MIEMBRO INFERIOR. By Alberto E. Laurence. Buenos Aires: Libreria y Editorial "El Ateneo," 1949.

[2] A COMPANION IN SURGICAL STUDIES. By Ian Aird, Ch.M., F.R.C.S. Baltimore: The Williams & Wilkins Co., 1949.

[3] BLOOD AND PLASMA TRANSFUSIONS. By Max M. Strumia, M.D., Sc.D.(Med.), and John J. McGraw, Jr., M.D. Philadelphia: F. A. Davis Co., 1949.

[4] STREPTOMYCIN AND DIHYDROSTREPTOMYCIN IN TUBERCULOSIS; REPORTS OF RESEARCH INCLUDING STUDIES SPONSORED BY THE AMERICAN TRUDEAU SOCIETY (MEDICAL SECTION, NATIONAL TUBERCULOSIS ASSOCIATION). Edited by H. McLeod Riggins, M.D., and H. Corwin Hinshaw, M.D. New York: National Tuberculosis Ass., 1949.

reference book for anyone who uses the drug or contemplates using it. JEROME R. HEAD.

THE first edition of *Human Pathology*[1] by Howard T. Karsner was published in 1926. Twenty-three years later the seventh edition has come to hand. The first edition contained 980 single column pages and 463 illustrations of which 20 were in color; the seventh edition contains 927 double column pages with 584 illustrations including 22 in color. Over the years this book has assumed a more and more important place among textbooks of pathology until gradually it has achieved pre-eminence. Students, professional pathologists, practicing physicians and surgeons have referred to it for accurate information about the known facts of the broad field of pathology and have always found the information they wanted or a reference which filled their need. Dr. Karsner has always put into his book the best of the old and the most promising of the new. His most recent additions include 2 excellent, new chapters, which contribute greatly to the usefulness of the book. One is on diseases of the eye, which has been written by J. Lowell Orbison and John E. L. Keyes, and the other on diseases of the skin by Herbert Z. Lund. The chapters on infectious diseases and on liver have been largely rewritten and indeed there are signs that most of the chapters have been revised. The index, which was poorly done in the sixth edition, is once more excellent and the references are thoroughly up-to-date. A noteworthy feature is the excellence of the photographs of patients, organs, and microscopic sections which illustrate the book. These are beautifully reproduced, which fact reflects much credit on the publisher. Indeed the book is published in a most satisfactory manner with the exception of its size and weight. But have there ever been medical textbooks which fit easily to the hand?

The seventh edition of *Human Pathology* has appeared in the same year that Dr. Karsner has retired as professor of pathology, and director of the Institute of Pathology, Western Reserve University. It is indeed a fitting memorial to his years of teaching, investigation, and writing in the institute which he founded and raised to maturity. All of his many students will be more than ever proud of "the Chief," and in the opinion of this particular former student—be it prejudiced or not—*Human Pathology* is more than ever the best book of its kind in our language. WILLIAM B. WARTMAN.

WITH the collaboration of Dr. Stack, Dr. Magnuson has brought out a new edition of his justly popular textbook on fractures and dislocations.[2] This is an excellent treatise for both medical students and practitioners.

In the first chapter, there is a description of fundamentals including calcification and emergency treatment. Throughout the book, the practical side of the treatment of fractures is emphasized. The more frequent fractures and dislocations of the body are considered in a regional manner and the treatment of each is described. The illustrations consist for the most part of roentgenograms and photographs with a moderate number of drawings. We believe that they are unusually well chosen.

This book also includes an authoritative chapter on fractures of the skull by Loyal Davis and one on physical therapy in the treatment of fractures by John S. Coulter.

For its size (521 pages) it contains an unusually large amount of useful information and we have no hesitancy in recommending it both to students and to practitioners. J. ALBERT KEY.

THE special field of hypertension with its ever-changing concepts of etiology and approach to therapy has necessitated the complete revision of chapters and numerous additions to the subject matter as presented in the second edition of the volume entitled *Arterial Hypertension; Its Diagnosis and Treatment*.[3] The book, though primarily designed for the physician who is undertaking the care of the patient suffering from hypertension, should be enlightening to physicians in all fields of medicine for the problem of hypertension invades every specialty. In the second edition a chapter has been added which is concerned with the diagnosis of hypertension due to known or attributable causes. This is extremely important because it is only in this sphere where a definitive cure may be expected and the diagnosis can only be made by *careful* laboratory and clinical investigation. Special emphasis has been placed on the newer psychosomatic approach to the problem of essential hypertension—an approach which, though realized for many years, has not been clearly delineated. The present status of the surgical treatment of hypertension is comprehensively reviewed and the authors have wisely allowed the reader to draw his own conclusions, in the light of the present published evidence, regarding this particular approach to treatment of the disease which after several years of enthusiastic support in several surgical circles now demands closer scrutiny and further evaluation.

There is a good discussion of dietotherapy in hypertension, particularly the rice diet which, during the past few years, has been riding the crest of popular appeal both to the laity and the medical profession, but is now being relegated to the ranks of the modified diet that eliminates specific substances known to be harmful in certain types of hypertension and its complications.

The end results of arterial hypertension in the peripheral vessels, heart, kidney, and brain are each

[1] HUMAN PATHOLOGY. By Howard T. Karsner, M.D., LL.D. 7th ed. Philadelphia, London, Montreal: J. B. Lippincott Co., 1949.

[2] FRACTURES. By Paul B. Magnuson, M.D., F.A.C.S., and James K. Stack, A.B., M.D., F.A.C.S. 5th ed. Philadelphia, London, and Montreal: J. B. Lippincott Co., 1949.

[3] ARTERIAL HYPERTENSION; ITS DIAGNOSIS AND TREATMENT. By Irvine H. Page, M.D., and Arthur Curtis Corcoran, M.D. 2d ed. Chicago: The Year Book Publishers, Inc., 1949.

discussed individually as to pathogenesis, diagnosis, and treatment. These complications of the disease are presented in a clear precise manner but in view of their importance could stand a more complete discussion. The present trend of the medical treatment of hypertension has been brought up to date, particularly by a discussion on the pyrogen treatment of the malignant phase. An appendix on methods of functional examination of the kidney, with a description of the techniques used in the more precise methods of evaluating renal function, should be of great aid in transplanting these procedures from the research laboratory.

In this new volume the authors have done an excellent piece of work in organizing and presenting, in compact form, modern concepts in the field of such an elusive disease as arterial hypertension.

HOWARD A. LINDBERG.

AN example of the trend in medical publications toward the monographic form is presented by *Diseases of the Aorta*.[1] The reasons for this development in medical literature are obvious. The sum of medical knowledge in many fields has become so great that it is no longer possible to cover many subjects adequately in the standard type textbook. Certainly all aspects of the aorta and its diseases have never been presented so thoroughly and yet so concisely as they have been in this monograph by Dr. N. E. Reich.

As pointed out by Dr. Dock in the foreword, the author has successfully resisted all temptation to stray from his subject. The monograph is extremely well organized. Each subject is discussed thoroughly but concisely. Repetition of subject matter has been carefully avoided by reference to other chapters whenever possible. Each chapter is accompanied by an excellent bibliography of source material.

The chapter on congenital anomalies involving the aorta is particularly good and especially pertinent at the present time, since recent advances in vascular surgery permit successful surgical correction of most of these lesions. Atherosclerosis of the aorta, syphilis of the aorta, aneurysms of the aorta, and occlusion of the aorta are discussed fully. However, the author tends to take a somewhat more optimistic view of the treatment available for these lesions than is warranted at the present time, particularly in regard to the surgical treatment of aneurysms.

The chapter on the procedures available for the diagnosis of diseases of the aorta is excellent.

This monograph is a worth while addition to medical literature and can be read with profit by the general practitioner as well as by those particularly interested in vascular diseases and their management.

O. T. CLAGETT.

[1] DISEASES OF THE AORTA; DIAGNOSIS AND TREATMENT. By Nathaniel E. Reich, M.D., F.A.C.P. New York: The Macmillan Co., 1949.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

QUINIDINE IN DISORDERS OF THE HEART. By Harry Gold, M.D. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1950.

PRACTICAL NEUROLOGICAL DIAGNOSIS; WITH SPECIAL REFERENCE TO THE PROBLEMS OF NEUROSURGERY. By R. Glen Spurling, M.D. 4th ed. Springfield, Ill.; Charles C Thomas, 1950.

LORD LISTER; HIS LIFE AND DOCTRINE. By Douglas Guthrie. Baltimore: The Williams and Wilkins Co., 1949.

MITCHELL-NELSON TEXTBOOK OF PEDIATRICS. Edited by Waldo E. Nelson, M.D. 5th ed. Philadelphia and London: W. B. Saunders Co., 1950.

EL INJERTO DE PIEL TOTAL EN LA REPARACION DE HERNIAS Y EVENTRACIONES ABDOMINALES; INDICACIONES, TECNICA QUIRURGICA, RESULTADOS. By Dr. Manuel Jose Vazquez. Buenos Aires: Lopez & Etchegoyen, 1949.

TRAINING FOR CHILDBIRTH; A PROGRAM OF NATURAL CHILDBIRTH WITH ROOMING-IN. By Herbert Thoms, M.D. 1st ed. New York, Toronto, London: McGraw-Hill Book Co., Inc., 1950.

COLLECTED REPRINTS OF THE DEPARTMENT OF OPTHALMOLOGY, West China Union University College of Medicine and Dentistry, 1938 to 1945. Chengtu, Szechwan, China: West China Union University, 1950.

MENSTRUATION AND ITS DISORDERS; PROCEEDINGS OF THE CONFERENCE HELD UNDER THE AUSPICES OF THE NATIONAL COMMITTEE ON MATERNAL HEALTH. Edited by Earl T. Engle. Springfield, Ill.: Charles C Thomas, 1950.

SURGICAL TREATMENT FOR ABNORMALITIES OF THE HEART AND GREAT VESSELS. By Robert E. Gross, M.D. Springfield, Ill.: Charles C Thomas, 1950.

PROCEEDINGS OF THE FIRST ANNUAL SYMPOSIUM ON ORTHOPEDIC APPLIANCES UNDER THE AUSPICES OF THE SARAH MELLON SCAIFE FOUNDATIONS MULTIPLE FELLOWSHIP. Washington, D.C.: Orthopedic Appliance and Limb Manufacturers Ass., 1950.

OPERATIVER DAUMENERSATZ UND BESEITIGUNG VON GREIFSOERUNGEN BEI FINGERVERLUSTEN. By Prof. Dr. Med. Otto Hilgenfeldt. Stuttgart: Ferdinand Enk, 1950.

CHIRURGIE DES PANCREAS. By Dr. Med. Walter Hess. Basel: Benno Schwabe & Co., 1950.

CONTRIBUCION AL TRATAMIENTO QUIRURGICO DEL CANCER DEL COLON DERECHO. By Jaime PiFigueras. Barcelona, Madrid, Buenos Aires, Mexico, Rio de Janeiro: Salvat, 1949.

CURRENT THERAPY 1950; LATEST APPROVED METHODS OF TREATMENT FOR THE PRACTICING PHYSICIAN. Edited by Howard F. Conn, M.D. Philadelphia and London: W. B. Saunders Co., 1950.

COMPULSORY MEDICAL CARE AND THE WELFARE STATE. By Melchior Palyi. Chicago: National Institute of Professional Services, Inc., 1950.

RESEARCH IN MEDICAL SCIENCE. Edited by David E. Green, Ph.D., and W. Eugene Knox, M.D. New York: The Macmillan Co., 1950.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

FREDERICK A. COLLER, Ann Arbor, *President*
HENRY W. CAVE, New York, *President-Elect*

PRELIMINARY PROGRAM FOR THE 36th CLINICAL CONGRESS—STATLER HOTEL, BOSTON OCTOBER 23 TO 27, 1950

THE 36th Clinical Congress of the American College of Surgeons will be held in Boston, October 23 to 27, with headquarters at the Statler Hotel. Meeting rooms in the Statler Hotel, Copley-Plaza Hotel, Mechanics Hall, John Hancock Auditorium, and Symphony Hall will be used to accommodate the sessions. Mechanics Hall will house the extensive exhibit of medical and hospital supplies and equipment, in addition to television and medical motion picture showings, and registration for surgeons and hospital representatives.

SURGICAL CLINICS AND TELEVISION

Surgical clinics are being scheduled in some twenty Boston hospitals. Color telecasts of surgical procedures at one of the hospitals will be shown daily during the Congress. Smith, Kline and French Laboratories of Philadelphia is furnishing the equipment for the color television and is arranging for its operation. With the aid of the same sponsor, the color television at the Clinical Congress in Chicago last year was so successful that it was featured in articles in many newspapers and magazines.

COMMITTEE ON ARRANGEMENTS

Heading the committee on local arrangements for the Clinical Congress is Dr. Thomas H. Lanman of Harvard Medical School. His committee and the hospital committee which he has appointed to arrange the surgical clinics are enthusiastically proceeding with plans for an outstanding Congress. Boston was host to the Clinical Congresses of 1915, 1922, 1928, 1934, and 1941, all of which were exceptionally successful and interesting meetings. Surgeons and hospital representatives from all parts of the United States, Canada, and other countries will be attracted to the 1950 Congress in Boston by the excellent programs that the city's 3 medical schools and 24 approved hospitals are helping to arrange. Hospital and surgical leaders of national and international fame will address the sessions, and many of them will be from the host city, which has always been noted for its medical leadership.

MEDICAL MOTION PICTURE PROGRAM

The Medical Motion Picture Committee is now choosing films which are to be shown at the Clinical Congress. Films which have been recently produced should be forwarded to the College for immediate review as it is the policy to include in the Clinical Congress program only those films which were submitted in time to obtain approval by the Committee on Medical Motion Pictures. The showings of medical motion pictures at the Clinical Congress are one of the leading attractions and are well attended.

SCIENTIFIC SESSIONS

A general assembly for both surgeons and hospital personnel will be the opening session on Monday morning, October 23. Scientific sessions will be held on Tuesday, Wednesday, and Thursday evenings. General surgery panel discussions are planned for the first 4 afternoons. Friday afternoon will be devoted to panel discussion sessions for 6 special fields of surgery as follows: orthopedic surgery, plastic surgery, urological surgery, thoracic surgery, neurological surgery, and obstetrics and gynecological surgery. Special sessions, including evening meetings, will be arranged for ophthalmology and otorhinolaryngology.

The Forum on Fundamental Surgical Problems will be held again in 1950 to give special opportunity for the presentation of the newest discover-

ies resulting from research, particularly by the younger surgeons. Brief reports of original clinical and experimental observations relating to the broad aspects of surgery and the surgical specialties will be given.

Symposia on cancer and on trauma will, as usual, be included in the scientific program.

ADVANCE PROGRAM OUTLINES

A tentative outline of the subjects for the afternoon panel discussions follows:

October 23, 1:30–3:00 Transthoracic Approach to Subdiaphragmatic Lesions
3:30–5:00 Cancer of the Uterus
October 24 1:30–3:00 Anesthesia
3:30–5:00 Reconstructive Surgery of the Hand
October 25 1:30–3:00 Surgical Treatment of Congenital Anomalies of the Digestive Tract
3:30–5:00 Pitfalls in Surgery of the Gallbladder and Biliary Ducts
October 26 1:30–3:00 Acute, Nontraumatic Conditions in the Abdomen

The moderators of these 7 panel discussions will be B. Noland Carter of Cincinnati; John C. Burch of Nashville; Wesley Bourne of Montreal; Henry C. Marble of Boston; Lawrence Chaffin of Los Angeles; Waltman Walters of Rochester, Minnesota; and Fred W. Rankin of Lexington, Kentucky.

The evening sessions on October 24, 25, and 26, in general surgery, will include the following subjects:

October 24 The Concept of the General-Adaptation-Syndrome as Applied to Surgical Problems (with special emphasis upon Cortisone and ACTH)
Biophysics in Surgery
The Principles Involved in the Clinical Use of Streptokinase-Streptodornase
October 25 Fracture Oration
Intravenous Fat Feeding
The Neurological Complications of Spinal Anesthesia
October 26 Lobotomy versus other Operations for the Relief of Intractable Pain
The Etiology and Treatment of Hirschsprung's Disease
Late Surgical Complications following Irradiation of Pelvic Viscera

OFFICIAL MEETINGS

A meeting of the Governors of the College is planned on Sunday afternoon, October 22. They will also meet for luncheon on Wednesday.

Dr. Frederick A. Coller of Ann Arbor, the outgoing President, will deliver the Presidential address at the Presidential Meeting on Monday evening. At the same session Dr. Henry W. Cave of New York will be installed as President, and Dr. Warren H. Cole of Chicago and Dr. G. Gavin Miller of Montreal as First and Second Vice President respectively. The Presidential Meeting is scheduled for the Ballroom of the Statler Hotel.

The annual Convocation which includes formal initiation ceremonies for the new Fellows will take place on Friday evening, October 27, probably in Symphony Hall.

The Annual Meeting of Fellows will be held on Thursday afternoon.

HOSPITAL CONFERENCES

The twenty-ninth Hospital Standardization Conference will convene during the first 4 days of the Clinical Congress. Its opening meeting will constitute the first formal session of the Congress and will be for both surgeons and hospital representatives. Hospital administrators, trustees, members of medical staffs, nurses, technicians, dietitians, and heads of the various hospital departments and their personnel, are invited to participate in the discussions at the conferences which will be directed by leading authorities in the hospital field.

ADVANCE REGISTRATION

Surgeons who wish to attend the Clinical Congress should register in advance. Advance registration will greatly expedite the procedure of registering. No registration fee will be charged Fellows whose dues are paid to December 31, 1949. For endorsed Junior and Senior Candidates, the fee will be $5.00. Non-Fellows who after individual consideration are permitted to register, will pay a fee of $10.00. No registration fee will be required of initiates of the class of 1950.

HOTEL RESERVATIONS

It is desirable to make hotel reservations as early as possible. In making these, communications should be addressed to the Convention Bureau of the Boston Chamber of Commerce, 80 Federal Street, Boston 10, which will start booking reservations on June 1. It is important that you state that you will be attending the Clinical Congress of the American College of Surgeons. All hotel reservations, both for surgeons and hospital representatives, are to clear through the Convention Bureau. No correspondence should be sent directly to the hotels. A form for reservations will be enclosed in a letter to Fellows. Choice of hotels may be designated.

In addition to the headquarters hotels, the Statler and Copley-Plaza, there are a number of first-class hotels within a short distance of headquarters.